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Original Communications

INFANTILE MORTALITY AND BACTERIOLOGIC INVESTIGATIONS OF THE EFFECT OF PROLONGED LABOR ON THE BABY

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THE past decade has witnessed a definite reduction in the maternal mortality rate of the United States and, it may be said, that this decrease has been recorded in almost all areas of the country. An analysis of the factors responsible for this noteworthy improvement in American obstetrics, as applying to the maternal end results, reveals, we believe, that more adequate teaching of medical students, better hospital training of graduates, and concerted efforts by federal, state, county, and city organizations, both lay and professional, are among the major causes. Unfortunately, however, no comparable reduction in fetal or neonatal mortality has been accomplished; perhaps because attention often has been focused upon the maternal results, almost to the exclusion of consideration for the offspring. We are of the opinion that the next decade should witness equally concerted efforts, on the part of all concerned, to reduce fetal mortality.

In this paper we shall employ the term "infantile mortality" to include all full-term and premature (1,500 to 2,500 Gm.) infants, still-born, or dying within fourteen days following birth. During the past ten years we have made determined efforts to reduce infantile

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mortality, and we have investigated the cause of infant deaths that have not been explained by trauma, congenital abnormality, asphyxia, maternal disease or some other known cause. Most of the clinical reports that appear in the literature on this subject include a relatively large number of infantile deaths that are not adequately explained. In 1934 we started taking blood cultures from the heart of stillborn infants immediately following delivery. As time progressed it became evident that the great majority of positive blood cultures were in infants born following prolonged labor where there was definite clinical evidence of intra-partum infection. In the first section of this paper we shall present a brief summary of our infantile mortality and various associated factors. In the second section we shall review a group of babies who had positive blood cultures at the time of delivery.

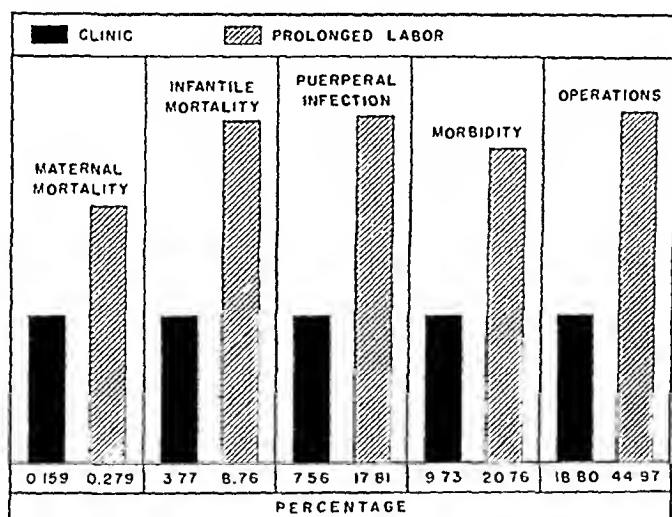


Fig. 1.

Material

In the period Sept. 1, 1932, to Aug. 1, 1942, there occurred 25,574 term and premature deliveries in the service of the Lying-in Hospital. There were 73 maternal deaths, or a rate of 2.64 per thousand deliveries. If maternal deaths of patients admitted post partum and deaths occurring in the home are omitted, the total number of maternal deaths is reduced to 67 and the rate to 2.42 per thousand deliveries. If patients dying before delivery, abortions, home delivery, and patients admitted post partum are excluded, there remain 44 deaths, or an incidence of 1.59 per thousand deliveries. There were a total of 1,041 (3.77 per cent) infantile deaths. The morbidity was 9.73 per cent and the incidence of puerperal infection 7.57 per cent.

For reasons previously stated, our attention has been primarily directed to the study of prolonged labor, which we arbitrarily have defined as labor lasting more than 30 hours. Consequently, we analyzed the percentage incidence of puerperal infection, maternal morbidity, maternal mortality and infantile mortality for labors of 30 to 36 hours,

37 to 48 hours, 49 to 60 hours, and for labors longer than 60 hours where delivery terminated spontaneously as well as by operative means. It at once became apparent that there is an increase in all of these factors as the duration of labor is increased, but even more marked is the difference between the incidence of these various factors between the spontaneous and operative groups. The latter group has an incidence of puerperal infection and morbidity of two to nearly four times that of the former, while the number of maternal and infantile deaths is greatly increased in the operative group.

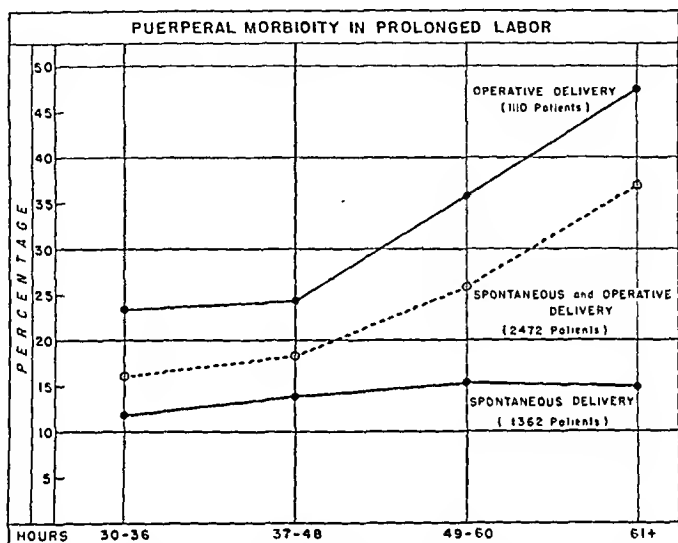


Fig. 2.

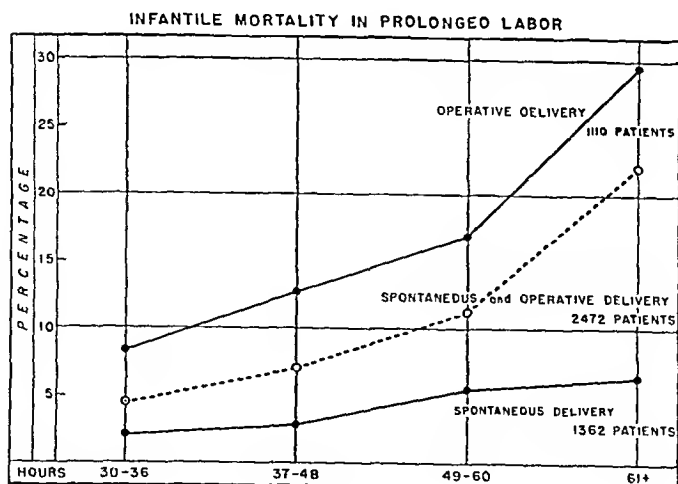


Fig. 3.

Fig. 1 illustrates graphically the great increase in maternal mortality, infantile mortality, puerperal infection, morbidity and the operative incidence in prolonged labor as compared to the incidence of these factors in the Clinic as a whole. The complications referred to are, in gen-

eral, more than twice as frequent in the prolonged labors as compared to the incidence in the Clinic as a whole. Fig. 2 shows that the great increase in puerperal morbidity is due chiefly to a very large increase of morbidity in the operative deliveries, while the increase in the spontaneous deliveries is relatively small. From a numerical point of view these curves are constructed from data that are quite comparable. The dotted line on this chart illustrates the combined rate for both the spontaneous and operative deliveries and demonstrates that the increase is caused primarily by the high rate in the operative group. It will be noted in general that the increase is not very marked prior to the elapse of 48 hours after the onset of labor. A very sudden increase occurred in the labors lasting 49 to 60 hours and a still further increase in those labors lasting longer than 60 hours. Fig. 3 illustrates the infantile mortality in labors lasting longer than 30 hours and the curves are quite comparable to those shown in the previous chart; namely, the number of infantile deaths in prolonged labors terminated by spontaneous delivery is relatively small in labors lasting up to 48 hours, and this number is only slightly increased where the labors extended up to 60 hours or even beyond that period of time. On the other hand, the upper curve in this graph shows a marked increase in infantile mortality where labor was terminated by operative means in the 30 to 60 hour group, and a steady increase in this rate until in the labors extending beyond 60 hours the mortality rate approaches 30 per cent. Again, the dotted line in the middle, which illustrates the infantile mortality in both spontaneous and operative deliveries, shows a definite increase which is caused largely by the deaths following operative deliveries. It is only fair to state at this point that the unfavorable results following the termination of prolonged labor by operative means may have been, in very many instances, absolutely necessary and unavoidable. Also, quite frequently, the baby was dead at the time the operative procedure was undertaken. On the other hand, the data illustrates graphically that the results are very much better if labor terminates spontaneously. This applies equally to mother and child. Accordingly, it would appear that prolonged labor per se should not be an indication for the operative termination of any labor.

A breakdown of the operative deliveries into three groups, namely, cesarean section, forceps, and breech, shows that in prolonged labor the incidence of cesarean section is approximately one-half that of the Clinic incidence as a whole. The frequency of forceps operations is approximately two and one-half times greater following prolonged labor as compared to that in the entire clinic, while the incidence of breech extraction is significantly increased. The infantile mortality following these three operative procedures in prolonged labor reveals a substantial increase following all three procedures, most marked in the forceps and breech extraction groups. It is significant to note at this time the relatively high infantile mortality following cesarean section in prolonged labors. Such indications for this operative procedure as premature separation of the placenta and placenta previa are very infrequently encountered in this group and, accordingly, are not the factors that would tend to increase the infantile mortality. It is also important to note that the mortality following forceps operations is more than four times as great where the labor is 60 hours or longer as compared to labors of 30 to 36 hours. The mortality following breech extraction amounts to one-third of all babies delivered by this means where the

labor lasts 60 hours or longer. This information is illustrated graphically in Fig. 4. The curve for cesarean section is omitted because of statistical unreliability owing to the small number of cases as compared to the relatively large number terminated by forceps and breech extraction.

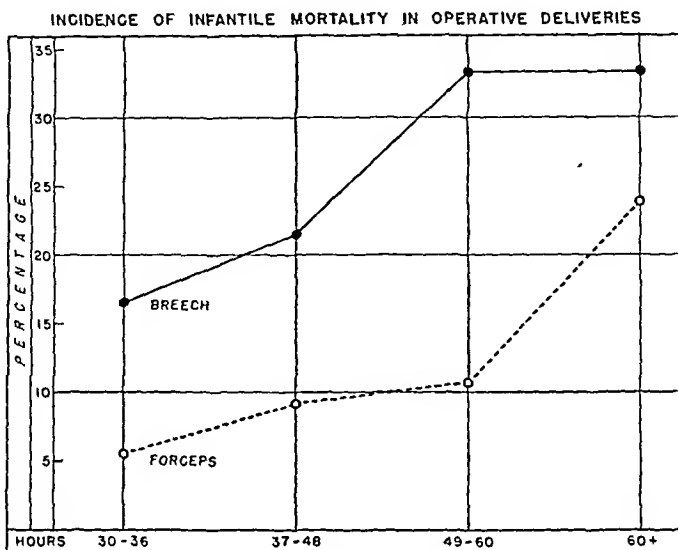


Fig. 4.

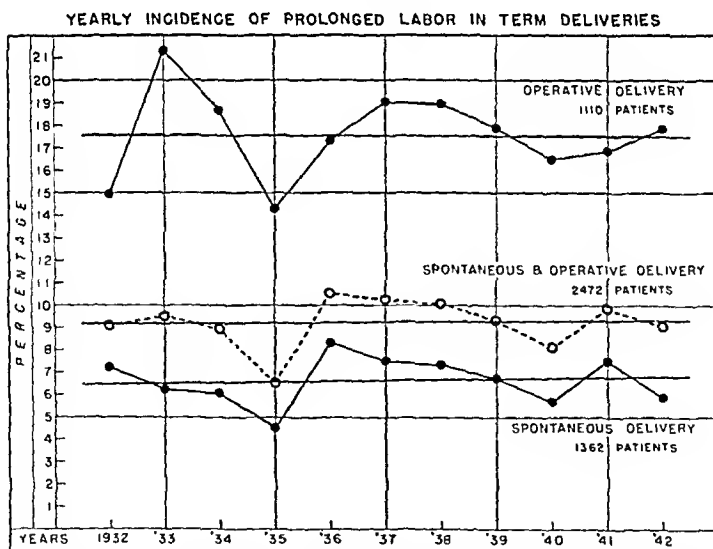


Fig. 5.

With this information at hand, which is quite disturbing, it becomes apparent at this point that we are not reviewing our good results but rather our experiences with some of our most trying obstetric problems. We will now proceed in an attempt to discover whether the incidence of prolonged labor is decreasing or increasing and whether the results are improving or not. Fig. 5 illustrates the yearly incidence of prolonged labor in term deliveries during the years from 1932 to 1942, re-

spectively. Observations for 1932 and 1942 do not cover the entire year, but they are calculated on a percentage basis and so are quite comparable. It may be seen, then, in Fig. 5 that the number of spontaneous and operative deliveries remains essentially the same throughout this ten-year period of time. The upper and the lower line illustrate the incidence in the operative and the spontaneous groups individually, and the middle curve represents the sum of both. The mean of each of these graphs is approximately a horizontal straight line. In other words, there has been no change during this period of time in the incidence of spontaneous or operative deliveries following prolonged labor.

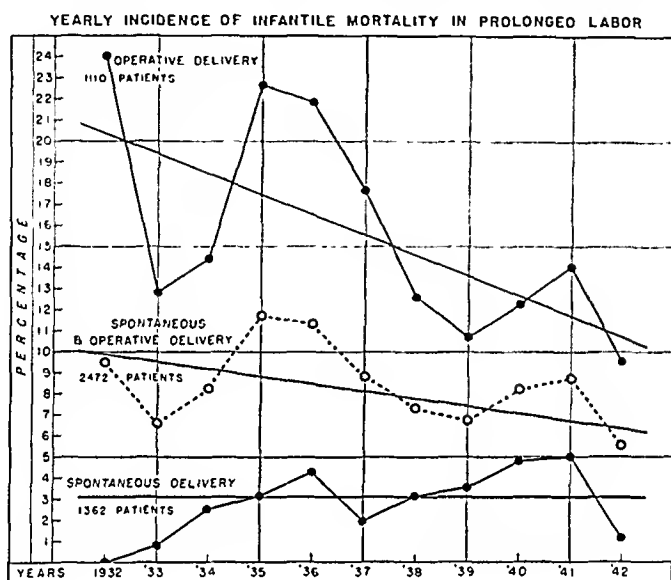


Fig. 6.

We then investigated the yearly incidence of infantile deaths in term deliveries following prolonged labor during the same period of time. This information is graphically illustrated in Fig. 6. It becomes apparent that the infantile mortality in spontaneous delivery following prolonged labor has remained relatively constant or increased slightly during this entire period of time and, in fact, this data may be expressed as a horizontal straight line. This is in marked contrast to the upper curve on this chart which illustrates the infantile mortality following operative delivery. A mean line which represents the approximate trend of this curve shows a very definite and progressive decrease from 1932 to 1942. This decrease is, accordingly, reflected in the combined curve represented by the middle dotted line and the decrease here is accounted for entirely by the decreased incidence of infantile mortality in the operative group. It then becomes evident that while the incidence of spontaneous and operative deliveries in prolonged labor remained constant, yet the incidence of infantile mortality in operative deliveries decreased significantly during the same time period.

In order to find a solution to this problem, we investigated the incidence of prolonged labor by years according to the duration of labor. Interestingly enough, the results of this investigation revealed that there was a significant decrease in the operative incidence in labors lasting 30

to 36 hours, as shown in Fig. 7, and a comparable significant increase as revealed in Fig. 8 in the operative incidence in the group with labors lasting 37 to 48 hours. Fig. 9 illustrates a smaller increase in the number of operative deliveries in labors lasting 49 to 60 hours, but no in-

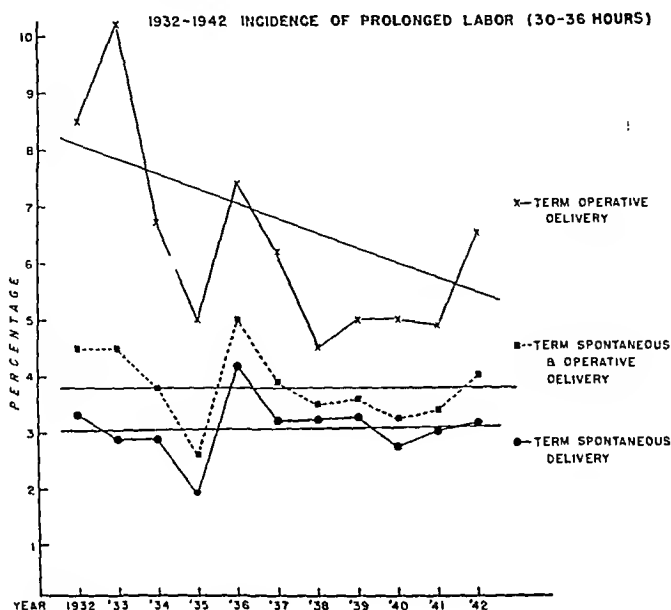


Fig. 7.

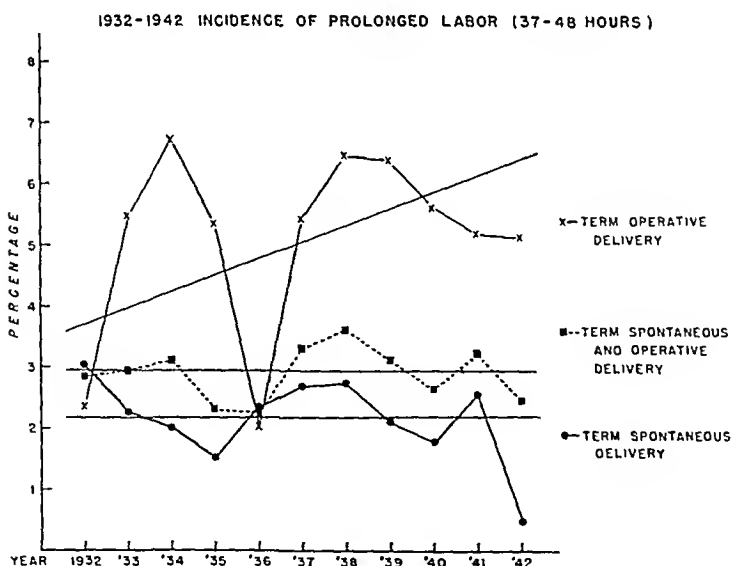


Fig. 8.

crease in the labors lasting longer than 60 hours, as is shown in Fig. 10. The interpretation of this information is quite interesting and would seem to suggest that we have tended to interfere less frequently in labors lasting 30 to 36 hours and somewhat more frequently in labors lasting 37 to 60 hours. What this probably means in actual practice is that

in the more recent years we have not interfered as frequently in the labors of 30 to 36 hours where possibly the cervix was incompletely dilated, but have awaited full or more complete dilatation of the cervix, and they were then included in the group whose labors lasted from 37 to 60 hours.

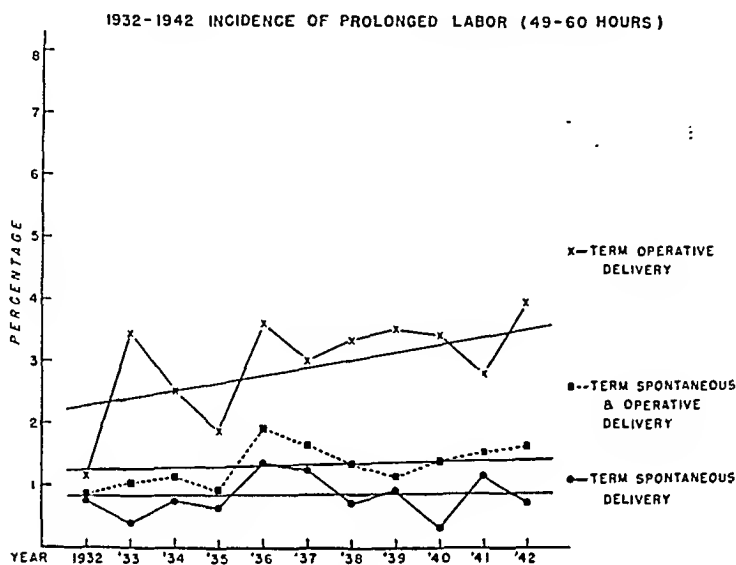


Fig. 9.

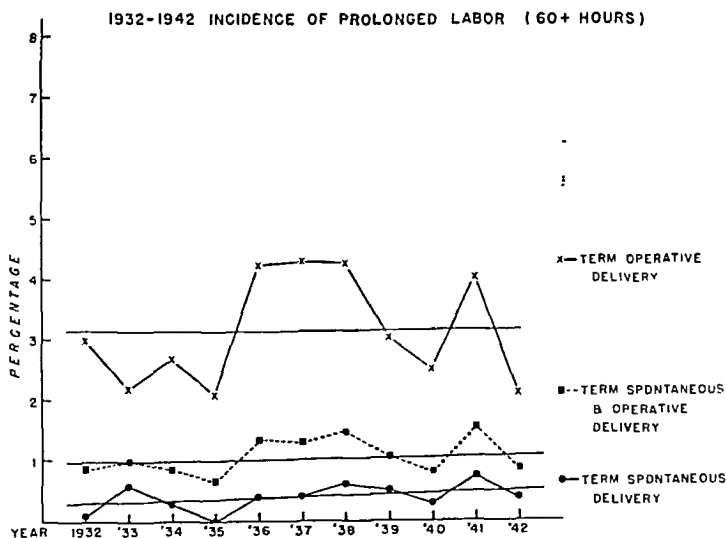


Fig. 10.

In general, it may be said as a result of studies of these data that prolonged labor per se exerts a deleterious effect on both the maternal and fetal organisms and the severity of this deleterious effect increased progressively with the duration of labor. Where labor is terminated operatively there is a superimposed effect caused by the procedure in question.

In the second section of this contribution we will attempt to find an explanation for the increased infantile mortality that is caused by the prolonged labor itself. All other factors may be wholly or partially excluded in this study. Prior to undertaking this investigation in 1934, we were impressed with the fact that during a prolonged labor the infant often died in utero where there was no serious disproportion or other traumatic factor that might explain the death of the baby. In fact, in many instances the syndrome of premature rupture of the membranes and desultory labor, followed by clinical evidence of infection in the vaginal discharge and in many instances an accelerated pulse rate and an elevated temperature appeared to be characteristic of this condition. Under these circumstances we have frequently observed the death of the fetus in utero and oftentimes the autopsy failed to reveal findings that would adequately explain the fetal death. It was for this reason that we decided to take blood cultures immediately following the delivery of stillborn infants. The technique employed consisted in preparation of the skin over the precordium with iodine and alcohol and a sterile needle attached to a 5 c.c. syringe was then inserted directly into the heart. It is usually possible to obtain blood or plasma in this manner for culture. The blood was inoculated into different media and incubated under both aerobic and anaerobic conditions. The subsequent identification of the organism present was carried out by recognized bacteriologic procedures.

We have employed the same technique in studying the blood obtained from babies that died following labors where there was an obvious cause for death, such as intracranial hemorrhage, congenital abnormality, asphyxia, et cetera, and this material serves as a control. It will not be detailed at this time other than to state that in the great majority of instances the cultures were sterile. We investigated a total of 140 babies where the blood cultures were negative and all available data indicate that there was usually some perfectly obvious cause of death. There was a total of 225 babies so studied and the blood cultures were positive for one or more organisms in 85 instances. Tables I to XI have reference only to this latter group.

Table I shows that of the 85 who had positive blood cultures, 83 of the infants were stillborn or deadborn, one was a neonatal death that occurred approximately 24 hours after delivery, and the other infant remained alive. A culture from this particular baby was obtained from the cord blood. In the second section of this table, it is seen that a definite intra-partum fever was present during the course of labor in 59 of the 85 mothers. In 26 there was no fever, but in many instances the vaginal secretions gave definite evidence of an intraovular intra-partum infection. The seriousness of this complication is illustrated by the fact

TABLE I

1. Total number of babies with positive blood culture	85
83 stillborn or deadborn	
1 neonatal death	
1 living	
2. Number of mothers with intra-partum fever:	
26 none	
3 low grade	
56 febrile	
3. Maternal deaths	3

that there were three maternal deaths in this group of patients, two of them caused solely by fulminating infections, while in the third patient the cause of death was not so clear. In Table II it is seen that the fetal heart stopped just prior to, during, or immediately following delivery on 20 occasions. In 16 instances the fetal heart stopped during pregnancy at various periods of time prior to the onset of labor, while in 47 instances the fetal heart stopped during the course of labor without apparent cause at an average time of seventeen and one-half hours before delivery.

TABLE II

a. Number fetal heart stopped during delivery	20
b. Number fetal heart stopped during pregnancy, i.e., before onset of labor	16
c. Fetal heart stopped an average of 17½ hours before delivery where the fetal heart was lost during labor	47

The question immediately arises as to whether there were any clinical factors that might explain these deaths. Table III illustrates such factors as might have been considered, but it is apparent that they were not necessarily related to the actual cause of the death of the baby. It is significant to note that no clinical cause could be found in 74 cases. It is quite possible that in the two instances of placenta previa and premature separation these factors may have been entirely, or at least

TABLE III. SUGGESTED CLINICAL CAUSES OF DEATH

	NO. CASES	PER CENT
Cord around neck	4	4.7
Toxemia	2	2.4
Placenta previa	2	2.4
Premature separation of placenta	2	2.4
*Unknown	74	87.1
Living	1	1.2
Total	85	

*Intrapartum infection.

in part, responsible for the death of four babies. Table IV illustrates the method of delivery in this group of infants, and it is seen that approximately one-third delivered spontaneously, while in two-thirds operative measures were employed. Approximately 25 per cent of the total group were delivered by means of forceps, 15 per cent by craniotomy, and 17 per cent by breech extraction. It must be recalled at this time, as was illustrated in Table II, that in 63 of the 85 babies involved the fetal heart had stopped prior to the actual delivery. Table V illus-

TABLE IV. METHOD OF DELIVERY

	NO. CASES	PER CENT
Spontaneous	30	35.3
Operative	55	64.7
Forceps	21	24.7
Craniotomy (vertex)	13	15.3
Voorhees bag, spont.	4	4.7
Breech extraction (preceded by bag, 6)	15	17.6
Version and extraction	1	1.2
Cesarean section (Porro)	1	1.2

trates the duration of labor and the length of time the membranes were ruptured prior to the time of delivery. It may be seen that in 26 cases the duration of labor was not prolonged, and in most instances in this group the fetal heart stopped prior to the onset of labor. On the other hand, in 58 cases, labor was of more than 30 hours' duration, the average being a little over 62 hours, and the membranes were ruptured an average of 63 hours before delivery. The table also shows the number of instances where the labor was 30 to 36 hours, 37 to 48 hours, 49 to 60, and 60 plus hours.

TABLE V. DURATION OF LABOR AND LENGTH OF TIME MEMBRANES RUPTURED PRIOR TO DELIVERY

NO. OF CASES	DURATION OF LABOR IN HOURS	AVERAGE LENGTH OF LABOR	AVERAGE NO. HOURS MEMBRANES RUPTURED PRIOR TO DELIVERY
26	0-29	12.7	28.4
10	30-36	33.2	53.7
10	37-48	40.6	46.8
13	49-60	54.5	56.5
25	60 +	86.7	76.8
58	30 +	62.3	63.0
84	0-60+	47.0	52.8

Table VI illustrates the autopsy findings. It is seen that an autopsy was performed on all infants excepting 12. As was previously shown in Table II, the fetal heart stopped during pregnancy and prior to labor in 16 cases, and an average of $17\frac{1}{2}$ hours before delivery on 47 occasions. Accordingly, the number of babies that were hopelessly macerated as far as the possibility of studying cellular pathology is concerned is relatively large. In approximately one-third of these babies no finding

TABLE VI. AUTOPSY FINDINGS

	NO. CASES	PER CENT
Maceration	28	32.9
Not macerated, no cause	4	4.7
Petechial hemorrhages	22	25.9
Pneumonia	13	15.3
Aspirated material in lungs	2	2.4
*Other	4	4.7
No autopsy	12	14.2
Total	85	

*Prematurity, congenital abnormality, etc.

other than maceration could be determined. It may have been in many of these instances that some significant change might have been discovered had it not been for the extensive maceration. In a considerable number of infants that showed petechial hemorrhage, fairly extensive maceration was also present. Furthermore, this condition is frequently encountered where babies die from asphyxia. The number of infants that actually had a definite pneumonitis was only 15 per cent, although it is quite possible that the incidence of this finding might have been considerably raised had it not been for the extensive maceration that was so frequently present. Interestingly enough, there was only one congenital abnormality that might have been responsible for the fetal death in the entire group.

The results of the histologic examination of the placenta is illustrated in Table VII. In over half of the placentas there was definite evidence of an acute and active infection. The placenta was normal in 17 per cent of instances, and in 12 per cent maceration was quite extensive. In five cases no sections were studied microscopically. The other findings in this table appear to have no practical bearing on the subject in

TABLE VII. HISTOLOGIC EXAMINATION OF PLACENTA

	NUMBER	PER CENT
Placentitis	44	51.76
Normal	15	17.53
Maceration	10	11.65
No section	5	5.88
Degeneration	5	5.88
Retroplacental hematoma	2	2.4
Other (prematurity, syphilis, etc.)	4	4.7
Total	85	

question. Table VIII illustrates the results of cultures, and it is seen that in 66 instances a single organism only was recovered from the blood of the infant. The predominant organism was an anaerobic streptococcus. In 19 instances more than one organism was isolated, and again, the frequency of the finding of anaerobic streptococci is apparent. It is important to note that a careful study of all of these organisms reveals their similarity to strains that may be isolated from the vagina at the onset of, or during, labor. The important exceptions are the presence of the colon bacillus, *Staphylococcus aureus*, *H. influenza*, and *Bacillus proteus*. An analysis of the circumstances where these organisms were recovered revealed either repeated vaginal examinations,

TABLE VIII. RESULTS OF CULTURES OF HEART BLOOD

	CASES	PER CENT
<i>Single Infection</i>		
Anaerobic streptococci	25	29.4
Diphtheroids, aerobic + anaerobic	9	10.6
<i>Streptococcus viridans</i>	8	9.4
Aerobic nonhemolytic streptococcus	7	8.1
<i>Staph. albus</i>	6	7.1
<i>B. coli</i>	5	5.9
Hemolytic streptococcus (alpha prime)	3	3.5
Anaerobic staph.	2	2.4
<i>Staph. aureus</i>	1	1.2
	66	
<i>Mixed Infection</i>		
Anaerobic strept. + <i>B. coli</i>	3	3.5
Anaerobic strept. + diphtheroids	3	3.5
Anaerobic strept. + <i>B. coli</i> + <i>S. albus</i>	2	2.4
Anaerobic strept. + <i>Strept. viridans</i>	2	2.4
Other	9	10.6
(combinations of two or more of the following organisms:	—	
Aerobic nonhemolytic strept., <i>B. proteus</i> , diphtheroids, <i>Strept. viridans</i> , anaerobic strept., unidentified gram-negative bacillus, <i>S. albus</i> , <i>H. influenza</i> , <i>B. coli</i> , anaerobic staphylococcus)	19	

difficult operative procedures or maternal systemic infections that readily account for the presence of these organisms in the blood of the in-

TABLE IX. RESULTS OF CULTURES OF HEART BLOOD INCIDENCE OF INDIVIDUAL ORGANISMS

	NO.	PER CENT
Anaerobic streptococci	41	48.2
Diphtheroids	13	15.3
<i>Streptococcus viridans</i>	13	15.3
<i>Staph. albus</i>	11	12.9
Aerobic nonhemolytic streptococcus	9	10.6
<i>B. coli</i>	11	12.9
Anaerobic staphylococci	3	3.5
Hemolytic streptococcus	3	3.5
Anaerobic gram-negative bacilli	2	2.4
<i>H. influenzae</i>	1	1.2
<i>Staph. aureus</i>	1	1.2

fant. Table IX shows the frequency with which individual organisms were found. The percentage incidence in this group will considerably exceed 100, because, as was illustrated in Table VIII, two or more organisms were isolated on 19 occasions. The data indicate that the anaerobic streptococcus is by far the most important organism concerned. It is our belief that in the circumstances under review these organisms are all potentially pathogenic with the possible exception of the *Staphylococcus albus*. It was recovered alone in culture on only six occasions, and accordingly, it is our impression that the great majority of these babies actually had a pathogenic organism present in their blood at the time of delivery.

In a considerable number of instances (47) specimens of uterine lochia obtained post partum were studied bacteriologically and Table X

TABLE X. ORGANISMS FOUND IN BOTH CULTURES, LOCHIA AND HEART BLOOD

	NO.
Anaerobic streptococcus	20
<i>Strept. viridans</i>	9
Aerobic nonhemolytic streptococcus	8
<i>B. coli</i>	5
Alpha prime streptococcus (hemolytic)	3
Anaerobic staphylococcus	2
<i>H. influenza</i>	1
<i>Staph. albus</i>	1

illustrates the organisms that were found in both cultures, namely, the heart blood of the child and the uterine lochia. Again, the anaerobic streptococcus plays the most significant role. The importance of the lower genital tract as a source of infection, namely, in causing first an intra-partum maternal infection and then an infection of the baby is obvious. Table XI illustrates the number of times there was a definite correlation of one or more organisms found in the heart blood and the

TABLE XI. CORRELATION OF ONE OR MORE ORGANISMS FOUND IN HEART BLOOD AND THE UTERINE LOCHIA

Uterine lochia not studied bacteriologically	38
Cases where uterine lochia was studied	47
Correlation	40
No correlation	7

uterine lochia. In 38 instances it was found that the uterine lochia was not studied bacteriologically and, accordingly, no correlation was possible. In the remaining 47 cases where a correlation was possible, it is seen to be present in 40 occasions and absent in only seven.

Discussion

Infantile mortality has shown no appreciable or significant reduction during the past ten years, such as has been accomplished in the maternal mortality rate throughout this country. The uncorrected infantile mortality rate in our clinic remains between 3 and 4 per cent. Prolonged labor, occurring in 9 per cent of our patients, plays a major role in this high death rate.

When prolonged labor terminates spontaneously, the incidence of puerperal infection is 9.01, 10.59, 13.11, and 11.70 per cent for the periods of duration of prolonged labor of 30 to 36, 37 to 48, 49 to 60, and 61 or more hours, respectively. The comparable incidences of morbidity for these periods are 11.70, 13.90, 15.30, and 14.89 per cent, respectively. On the other hand, when prolonged labor is terminated by operative means, the incidence of both puerperal infection and morbidity is doubled or trebled, the former being 20.57, 22.65, 32.82, and 43.00 per cent and the latter 23.43, 24.47, 35.90, and 47.50 per cent for each of the four periods of duration described above, respectively.

For these four periods of duration of prolonged labor, the infantile mortality rate in spontaneous delivery is 2.05, 2.86, 5.46, and 8.36 per cent, respectively; while in operative delivery the rate is 8.33, 12.68, 16.92, and 29.50 per cent, respectively.

The incidence of forceps delivery in prolonged labor is 35.51 per cent (compared to our total incidence of 14.94 per cent) with an infantile mortality of 10.88 per cent as compared with an infantile mortality rate in forceps delivery for the whole Clinic of 4.85 per cent. Breech extraction and cesarean section reveal equally unsatisfactory infantile mortality rates in the prolonged labor group, the former with 22.46 per cent (Clinic 13.47 per cent) and the latter 12.90 per cent (Clinic 9.8 per cent). An analysis of these unsatisfactory fetal results on the basis of the four periods of duration of prolonged labor (30-36, 37-48, 49-60, and 61 plus hours) shows that in forceps delivery the infantile death rate is 5.59, 9.23, 10.69, and 23.89 per cent, while in breech extraction the rate is 16.66, 21.56, 33.33, and 33.33 per cent for each of the periods, respectively.

A further analysis of our results in prolonged labor showed an appreciable decrease in the infantile mortality following operative delivery. The only explanation for this reduction appears to be the fact that we have tended to interfere less frequently in labors of 30 to 36 hours and slightly more frequently in those lasting 37 to 60 hours.

It is our feeling that the evidence presented strongly suggests the fact that organisms present in the vagina at the onset of labor become

invasive and pathogenic during the course of labor. Various reasons have been advanced by different investigators to explain this phenomenon. It is not our purpose, however, at this time to discuss this particular question. If other organisms are introduced into the vagina during the course of labor they also may play a role in the development of intra-partum infection. The rapidity with which this infection develops is greatly enhanced by early rupture of the membranes. At the same time, these studies indicate that the apparent intact membranes do not constitute an impassable barrier to such microorganisms as have

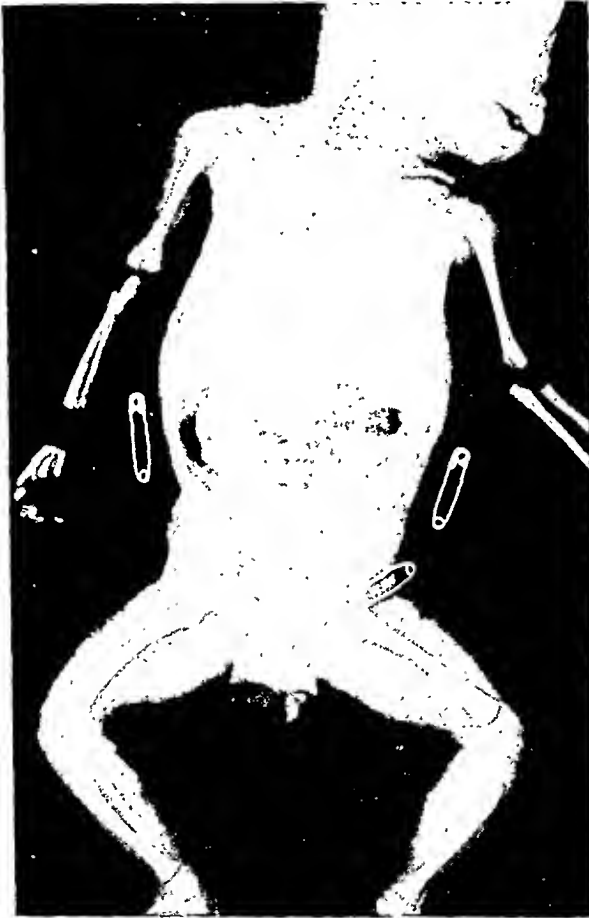


Fig. 11.

been discussed. The most frequent site of infection is first intraovular, then the fetal membranes, the placenta, and the maternal tissues. It appears probable that if the placenta is situated high in the fundus that it is most likely to be involved late in comparison with the placenta that is situated nearer the cervix. It would appear quite possible for these organisms to pass from the maternal portion of the placenta to the fetal circulation and thence to the baby. Another apparently common method of fetal invasion is the direct extension through the respiratory passages to the lungs where a pneumonitis develops. A third and long recognized

possible mechanism is illustrated in several of our patients where there was a maternal blood stream infection. Such an infection may extend from the maternal to the fetal blood through the medium of the placenta.

An analysis of the autopsy findings reveals that there was definite pathologic evidence of infection present in only about one-fifth of these babies. We are not prepared to state that the septicemia that we have reported or the mere presence of organisms in the blood stream was definitely responsible for the death of the baby. However, on the other hand, if there was no obvious clinical cause of death and a definite bacteremia was present, it would seem to suggest that the infection was at least the only possible etiologic factor known. Negative autopsy findings, especially in macerated infants, do not preclude the possibility of an extensive infection, as is illustrated in the following two cases.

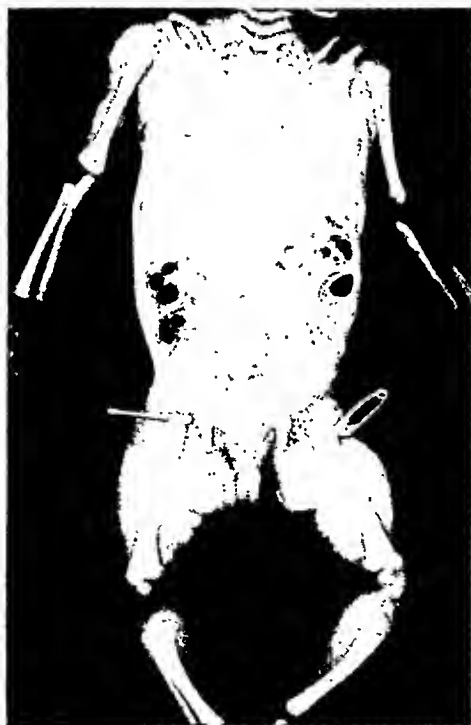


Fig. 12.


Fig. 11 is from an untouched roentgenogram taken shortly after the birth of a baby delivered following a labor of 105 hours where the membranes had ruptured prematurely. The fetal heart stopped twenty-four hours before delivery which was effected by an easy low forceps. The culture of the heart blood revealed an anaerobic nonhemolytic streptococcus and diphtheroids. The uterine lochia contained an anaerobic nonhemolytic streptococcus and *B. coli*. No cause of death or *significant* pathology was found at autopsy. The gas present in the intestines, heart, abdominal aorta, and in the large vessels of the extremities has undoubtedly been caused by the metabolism of the organisms present.

Fig. 12 was made from the film of a baby dying nine hours before delivery which terminated spontaneously following a sixty-five-hour labor where the membranes ruptured prematurely. Both uterine lochia and heart blood revealed an anaerobic nonhemolytic streptococcus on culture. Again, the autopsy findings were not significant excepting for extensive maceration, while the film reveals gas in the lungs, intestines, and large vessels. The evidence here adduced, of course, does not necessarily mean that the infection was acquired before the death of the baby. All or some of the gas formation may have developed in utero after the death of the baby.

When one attempts to rationalize the management of obstetric patients from the point of view of obviating this unfortunate possibility, it at once becomes evident that the most important single factor is to prevent prolonged labor. Unfortunately, our foresight on this subject is at times worth but little, while often in retrospect we wish that our management had been different. We recognize that infection starts coincidentally with every labor, that the rapidity with which it develops is enhanced if the membranes are ruptured. In the great majority of instances labor is terminated prior to clinical evidence of infection. However, approximately 9 per cent of labors are prolonged; and as soon as this complication is encountered the development of clinical intrapartum infection becomes a real possibility, and the unfavorable effects will be encountered in babies with increasing frequency as the duration of labor is extended. Unfortunately, the means at our disposal of predicting a long labor are not very reliable. Again, our methods of improving the quality of labor and shortening its duration are often not very effective. Medicinal stimulation, such as castor oil and quinine, may be of some help. Physical stimulation, such as hot enemas, hot drinks, massage of the fundus, et cetera, are at times helpful, but cannot always be relied upon. The use of oxytocics is usually not indicated. At times, good results have followed the employment of intranasal pituitary extract following the so-called medical induction, and possibly on rare occasions the same may be said of very small doses of the same drug injected intramuscularly where the patient is under the closest observation and supervision.

Another approach to this problem that certainly should be considered at this time would be the use of a sulfonamide drug during the course of prolonged labors. We have had the opportunity of studying some patients in this manner and, in general, our experience indicates that the drug is of little or no value if it is not employed until after the development of fever and a purulent vaginal discharge. On the other hand, we have observed a beneficial effect where the medication was given somewhat earlier in prolonged labors. It is necessary in such instances to make every effort to improve the quality of labor at the same time. The sulfonamide drug that we prefer at this time is sulfadiazine. It is imperative in patients who are receiving this compound that an adequate urinary output be maintained. Accordingly, it becomes most important

that accurate records of the urinary output be kept, and intravenous glucose should be employed if it is not adequate. An optimum output should be at least 50 and preferably 75 c.c. per hour. Recent evidence indicates that crystallization of the drug in the urinary tract may be avoided if sodium bicarbonate in large doses (4 Gm. every 4 hours) is administered at the same time. At times this latter medication may be contraindicated because of a toxemia and associated water retention.

It is our feeling that these considerations should be carefully evaluated before prematurely terminating a prolonged labor. It is difficult to know in any given case when infection is present in the baby. For reasons poorly understood fetal death may occur in some instances after 40 hours of labor, while in others it does not occur after the lapse of 100 hours under comparable conditions. Again, while the fetal death may be preceded by a rapid rate of the baby's heart, this is not always the case and the death in utero occurs without any prodromal signs. Radical procedures aimed at delivery before complete dilatation of the cervix so often result in extensive maternal trauma, causing blood loss and shock, spreading infection, and may in no way be compensated for by the birth of a living baby, because so often the babies are already infected and may die at the time of delivery or shortly thereafter. It may be that the presence of the fetal bacteremia explains the long recognized clinical fact that babies delivered following prolonged labor withstand any operative procedure very poorly. This all implies that if at all possible such labors should be terminated spontaneously. There will be many instances when this is impossible, but it would appear that we are not justified in undertaking relatively radical operative procedures where the main indication is the hope of obtaining a living baby. By adherence to this principle we will continue to lose some babies as a result of intra-partum infection and the subsequent fetal bacteremia, but we will not traumatize the mother and produce a state of shock and end up with a stillborn infant. We do not imply by these statements that there are not occasions when expert obstetric judgment and skill may be applied and labor terminated operatively with a happy outcome for both the mother and infant. 

Conclusions

1. The incidence of puerperal infection, total morbidity, maternal and infantile mortality increases progressively with the duration of labor, and in prolonged labor all are much increased when labor is terminated by operative means as compared to spontaneous delivery.
2. The incidence of prolonged labor has remained unchanged during the past ten years in the New York Lying-in Hospital.
3. Infantile mortality following prolonged labor has decreased steadily during the past decade. This decrease has been effected largely through a decreased rate following operative delivery.

4. The incidence of operative delivery following labor of 30 to 36 hours has decreased, while there has been an increase in operative delivery following labor of 37 to 60 hours. There has been no change in labors lasting more than 60 hours.

5. A fetal bacteriemia was found in 85 stillborn infants, most of whom were born following prolonged labor with intrapartum infection.

6. In the majority of these infants there was no pathologic lesion to explain the death, and the idea is advanced that infection may have been responsible.

7. The origin of the intra-partum infection was for the most part autogenous (from the maternal genital tract) and subsequently extended to the baby by various routes.

8. The anaerobic streptococcus (including facultative strains) was the most common organism found in the infant.

9. Efforts should be directed toward improving the character of contractions in desultory labors with a view to shortening the total duration of labor.

10. In general, operative procedures aimed at delivery following prolonged labor give poor results. The best results, on the other hand, follow spontaneous delivery.

11. Our recent but, as yet, limited experience indicates that sulfadiazine may prevent, to some extent at least, the development of intrapartum infection if employed relatively early in prolonged labor. On the other hand, if it is employed after the frank development of intrapartum infection, it has little or no therapeutic effect.

A FURTHER CONTRIBUTION TO THE SYNDROME OF FIBROMA OF THE OVARY WITH FLUID IN THE ABDOMEN AND CHEST, MEIGS' SYNDROME*

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IN 1937 in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Meigs and Cass¹ presented the histories of four patients who had ascites and hydrothorax associated with fibroma of the ovary and relieved of their serous fluids by removal of the tumor. No reasons were found that adequately explained the phenomenon. In the years following the first presentation of this syndrome, other cases were reported and brought to the authors' attention, so that in 1939 in the *Annals of Surgery*² 15 cases were summarized. Later, in 1940, in an

*Presented, by invitation, at a meeting of the New York Obstetrical Society, January 12, 1943.

article in Frank Howard Lahey's *Birthday Volume*,³ the total was brought to 18. The present report increases the number of authentic cases to 27. It is obvious therefore that this syndrome is of considerable importance, for some patients have died without proper surgical relief and some who were doomed because of considered inoperable malignancy are now well. In 1941 the senior author (J. V. M.) operated upon two patients and his associate, Langdon Parsons, operated upon another (Ritvo's⁴) on his service at the Poudville Hospital. Thus the occurrence of three lesions of this type in one year demonstrates effectively that it must always be considered in a differential diagnosis of abdominal and chest fluid. J. V. Breen and T. H. Nelligan⁵ have kindly allowed us to include in the synopses the history of their patient operated upon in the "House of Mercy Hospital," Pittsfield, Mass., on Nov. 15, 1940, and not as yet reported. In 1937 Muriel B. McIlrath^{5, 6} stimulated further investigation into the literature which resulted in the addition of two cases to the total, and again in June, 1942, she located a report by Lawson Tait in which he advocated exploring patients with abdominal and chest fluid for he considered that this combination did not always mean cancer. Thus the old adage is proved that "there is nothing new under the sun." Lawson Tait's⁷ discussion, somewhat abbreviated, is quoted below:

"L. T., single, aged 36, was sent to me by Dr. Brown of Tintern in January, 1890, with a large abdominal swelling. . . . About June, 1889, her abdomen was noticed to be enlarged. This steadily increased, very rapidly during December, 1889.

"For a month before admission she had severe cough, shortness of breath, and night sweats, with profuse expectoration of much black-colored stuff.

"Condition on admission (January, 1890)—body generally emaciated, abdomen greatly enlarged. She breathed rapidly and with difficulty. On examining the chest the left side was absolutely dull nearly up to the clavicle. There was no vocal fremitus or vocal resonance, the intercostal spaces were increased and bulged, the left side of the chest moved but slightly during respiration, and the heart was displaced to the right. There was evident hydrothorax of the left side.

"On examining the abdomen . . . there was all the physical signs of ascitic effusion free in the peritoneal cavity. In addition there could be felt on deep pressure through the fluid a large rounded solid tumor, apparently moored in the pelvis and floating freely in the ascitic fluid. As the breathing was much distressed the left pleural cavity was aspirated, and ninety-five ounces of blood-stained serum removed. A few days after the tapping of the left side fluid was discovered in the right pleura and was similarly removed. It contained a quantity of blood. The diagnosis of malignant disease of the peritoneum with secondary infection of the pleural surfaces was made. I declined to operate on the abdominal tumor, and the patient returned home to die.

"About a fortnight after returning home her left pleura was again tapped, and eighty ounces of pale yellowish fluid removed. In February, 1890 the abdomen was tapped, and eleven quarts of pale yellow thin ascitic fluid removed. From this time until February, 1891 her

abdomen was tapped over thirty times, from eight to fourteen quarts of thin clear yellowish fluid being removed at each operation. She was last tapped on February 28, 1891 when eleven and a half quarts were removed. The pleural effusions did not recur. The patient was readmitted on March 4, 1891; she was then in much better health. She had no pulmonary symptoms, and she was not so emaciated. The pleural effusion had not reappeared since the last thoracentesis in January, 1890.

"On examination there was an impaired percussion note over the base of the left lung behind, and distant breath-sounds. The abdomen was distended with free ascitic fluid, floating in which could be felt the solid tumor before described.

"There was no edema of the legs and no albumin in the urine.

"Operation on March 5th, 1891—I opened the abdomen by short vertical incision in the midline. As soon as the peritoneal cavity was reached a large quantity of ascitic fluid escaped. The tumor was now discovered to be a large solid growth of the right ovary. It was quite free from adhesions save to the ovary of the other side. The tumor was delivered through the opening, and the pedicle transfixed and tied. The ovary of the other side was so adherent that it was removed. The tumor was now cut away, a glass drainage-tube inserted, and the wound closed. About the fifteenth day her evening temperature began to rise, and she had pain in the back and pelvis. On examination a tense rounded fluctuating swelling was discovered behind the uterus. On the twentieth day this was aspirated per vaginam, and twelve ounces of thick offensive grumous pus removed. It was aspirated again on the twenty-sixth day when five ounces of pus were removed. Three days later the pus again accumulated. This time, however, it burst into the vagina spontaneously, and continued to discharge for about a week. After this her recovery was uninterrupted but slow.

"The tumor weighed 2 pounds 2 ounces. It was nearly globular in form and quite solid. Attached to it were the ovary of the other side and the Fallopian tube of its own side. Microscopic examination showed it to be a fibroma. On its free surface were a few small cysts containing clear fluid.

"The lesion in this case is, in my opinion, a very valuable indication that no set of conditions in the abdomen, however apparently unfavorable, are sufficient to justify us in an absolutely unfavorable condemnation in any particular case. Looking back upon my experience of pleural effusion as complicated by abdominal disease, which I have said probably gives the somewhat insignificant number of twenty cases out of more than three thousand, I think that probably my general impression that it is a very fatal complication, especially when the fluid is of a bloody character is correct; and if half of the cases had been submitted to abdominal section, simply for the purpose of exploration and removing the bulk of fluid, the likelihood is not great that permanent benefit would have accrued in many of them; but if one of the lives had been saved by the discovery of a mistake, I think it would have quite justified the performance of the incision in all the rest for under such circumstances the mere opening of the abdomen has risk very little, if any, greater than the process of tapping, which has to be employed for the purpose of giving the patient relief. Tapping, however, has the disadvantage that it leaves the condition of diagnosis quite as imperfect as it was before the operation, and I have never in a single instance seen anything like a curative effect from the

process of tapping in the abdomen. Even in the successful case I have given in detail, tapping of the pleura did not seem to have the controlling influence of preventing further secretion; whilst in the abdomen it has no curative influence at all, having had to be repeated over thirty times. The striking results obtained in this case by the correction of my initial mistake have gone a long way to confirm me in the advisability of extending the principles of exploratory and confirmatory incisions in the abdominal disease to an almost universal application."

The senior author's new cases and those reported in the literature since his last presentation give the usual history and have the same physical findings, dyspnea, abdominal pain, and an abdominal tumor. New suggestions have been made to explain the fluid but nothing of any real value has been suggested. We do not know why there is fluid in the abdomen. In Case 25 (M. R.), the peritoneum in the region of the tumor was definitely inflamed and covered with fibrin so it is possible to assume that the fluid may be an inflammatory exudate, but this is not probable for other patients have not had any signs of inflammation in their peritoneal cavities. Twists of the tumors are rare, and adhesions are not common. It must be admitted that there is no explanation at the present time, but a letter from Dr. Thomas S. Cullen written after reading the 1940 article in Dr. Lahey's Volume is of great interest. Dr. Cullen has an explanation and to date it is more satisfactory than any other, but probably it will in the end be proved as not correct. Below is a slightly modified copy of his letter:

"I am not at all surprised that you have long wondered as to what caused the accumulation of the abdominal fluid, particularly as microscopic sections invariably show an intact surface to the tumor and no evidence whatever of small round cell or polymorphonuclear infiltration. One gathers no clue whatever from the microscopic examination.

"In the early 90's Dr. Osler saw a patient who had been all over Europe and who had been tapped many times. He sent her to Dr. Howard A. Kelly and he removed a fibroma of the ovary and also a large quantity of abdominal fluid.

"Early in 1897, when resident on Dr. Kelly's staff, I operated on a patient with a solid ovarian tumor and much free abdominal fluid.

"You will note that prior to my operation 23 gallons of fluid had been drawn off from the abdomen in a little over two months.

"The patient recovered after the removal of a fibroma of the ovary and there was no further edema or abdominal fluid.

"Nearly every case of fibroma of the ovary that I have seen has been accompanied by abdominal fluid."

On pages 30 to 38 in Kelly and Cullen's *Myomata of the Uterus*, there are described seven cases with considerable fluid in the abdomen. The authors believe that torsion of the pedicles of the tumors is responsible and they also mention that torsion of the loose pedicle of an ovarian fibroma is the reason for ascites in such cases. Partial rotation of the tumor with twisting of the vessels is responsible for fluid in the others. In this volume on page 32 is the report of a colored woman of 36 who had, in addition to abdominal fluid definite chest fluid; 1,550 c.c. of fluid had been withdrawn from the chest cavity before operation. The

patient was considered to have, in addition to her fibroids, mitral insufficiency and chronic nephritis. She recovered without complications. It is obvious, in our present knowledge, that the chest fluid was due to the same condition that caused the ascites.

Fluid in the abdomen accompanying fibroma of the ovary is a frequent finding and has been reported in all series reported in the literature. The removal of the tumor does stop the formation of the ascites; therefore there is a direct cause and effect. However, inflammation, twists, and omental adhesions are not common and therefore are probably not the only reasons for the presence of fluid. Lack of drainage of the right chest by the azygos vein was suggested in our first article as a cause of right pleural effusion, but fluid also has been found in the left chest and in both and thus does not seem an adequate explanation. In Case 19 the patient died and at autopsy the azygos veins were examined and found to be very large. Whether this indicates that they were busy with drainage or were interfered with is not at all clear.

The alarm reaction of Selye¹⁰⁻¹² as suggested in 1939 may still be considered as neither proved nor disproved. In this explanation, arguing from data on animals, repeated minor trauma to the peritoneum by the fibroma causes a resistance of tissues which later return to normal but after a period of months with continued trauma the resistance disappears, and then there appears a histamine toxicosis or anaphylactic shock plus accumulations of peritoneal and pleural transudate. In experimental work such an explanation in certain animals with shock and serous exudates is possible but to explain this syndrome on the basis of such experimental findings cannot be done.

Serum protein determinations have been found normal in a sufficient number of cases to rule out edema due to this cause as an explanation. It is true that some patients have edema of the legs and lower body but this was not always the case. There is insufficient evidence to explain gross chest and abdominal fluid by protein lack.

Cardiac and renal conditions may account for accumulations of fluid, but the patients here reported did not have cardiac or renal disease.

One of the most interesting phenomena observed in some cases is the tremendous accumulation of fluid in the chest with only small amounts in the abdomen. It is almost as if there were an attraction in the chest for the abdominal fluid. The fluid may accumulate overnight after the chest has been tapped, there being as much in the chest as on the day before. The amount of fluid may be very great and a great many tapplings may have been carried out. Cachexia may appear, the patient being unable to keep up the supply of fluid, and dehydration and death may occur; yet the amount of fluid in the abdomen, the probable source of the fluid, may remain within limits easily compatible with life. The reverse may be true, as in Lawson Tait's case, but it is not so common.

Two patients operated upon in 1941 presented an opportunity to palpate the structure of the diaphragm, to collect fluids for investiga-

tion, and to show that particulate matter could pass from the abdominal fluid into the chest fluid. Case 24 was referred by Dr. H. H. Hamilton of Plymouth, Massachusetts with a diagnosis of Meigs's Syndrome. At operation a large opening was found in the diaphragm in front of the aorta connecting with the mediastinum. The question arose then whether or not fluid could pass from the abdomen into the right chest which contained fluid through this passage. A few days later one of the authors (J. V. M.) called upon Dr. William E. Ladd¹³ of the Children's Hospital in Boston and asked if such an opening was possible. Dr. Ladd felt that a passage from the abdomen into the chest, a so-called pleuroperitoneal canal was a definite possibility but that it probably was not often compatible with adult life.

In an article written by Ladd and Gross,¹⁴ in 1940, they say "The situations in the diaphragm where congenital hernia occurs are the left and right sides posteriorly, where the defect is due to a persistent pleuroperitoneal canal (the foramen of Bochdalek), the esophageal opening, or the substernal opening commonly referred to as the foramen of Morgagni, of these hernias that occurring in a persistent pleuroperitoneal canal is by far the commonest. The fact that the hernia through the esophageal hiatus is commonest in adult life is due to the high mortality in infancy of patients with a hernia through the pleuroperitoneal canal."

In other words it is not likely that pleuroperitoneal canals exist in adult life, therefore the combination of a fibroma of the ovary and a pleuroperitoneal canal could not be so common as the syndrome under discussion seems to be. Harrington,¹⁵ in 1942, in discussing diaphragmatic hernia in children, lists 6 of 21 as being of the type of hiatus pleuroperitoneal; yet in a list of diaphragmatic hernias in adults in the same article he finds but two in 283. In other words this type of hernia with direct opening from the peritoneum to the pleural cavity is rare, most children with it having died until the more modern operations of Ladd and of Harrington. In discussing our problem with Dr. Richard Schatzki¹⁶ of the roentgenologic department of the Massachusetts General Hospital he pointed out that Lamb¹⁷ states that at an autopsy on a 33-year-old man he found absence of the diaphragm in small areas with viscera in the chest cavity. These were not true hernias as there was no peritoneal sac, but an opening through the diaphragm. In his patient there was also absence of the pericardium. It is possible therefore that a continuation of the peritoneal pleural opening without intervening hernial sac can occur. An autopsy of a patient with a pleuroperitoneal canal is described, and Ladd and Gross admit its possibilities, and Harrington has operated upon two adult patients with such an abnormal diaphragmatic development. It is clear, however, that the rarity of this condition of the diaphragm makes it very unlikely that in the 27 patients with ascites and fluid in the chest and a fibroma of the ovary that such an opening could be present. A chance to verify this possibility came with the next patient (Case 25) referred by Dr. E. D. Churchill and operated upon in the Baker Memorial Hospital of the Massachusetts General Hospital. At operation the diaphragm was carefully explored and no opening found. A small opening could not be ruled out by palpation of the diaphragm from a lower abdominal incision but certainly no opening of any considerable size existed.

During the preoperative investigation of Case 25, fluid was removed from the chest cavity and 600 c.c. of air introduced into the pleural

cavity. The patient was then placed on the tilt table in the x-ray department with the hope that air might be forced from the chest into the abdomen through a possible pleuroperitoneal canal or any other opening, but the x-ray report which follows shows that: "there was a large quantity of air in the right pleural cavity. There was considerable fluid remaining. The patient was tilted into Trendelenburg position so that the air in the pleural cavity came in contact with the diaphragm. She was then placed on each side and back, films being taken to show free air in the abdomen in each position. There was no free air in the abdomen. The gas bubble in the fundus of the stomach was in normal position. There was no evidence of hernia. By x-ray, therefore, as well as by palpation no evidence of a canal could be found in this patient. In Case 26, reported by Ritvo,⁴ the patient was peritoneoscoped previous to operation and a good deal of air was pumped into the abdomen to a point of discomfort and dyspnea in an effort to demonstrate any passageway for air from the abdomen to the thorax. After the peritoneoscopy, the air pressure was released to make the patient comfortable and a good deal purposely left in the abdominal cavity. Immediate x-rays were taken to demonstrate the presence or absence of air in the thorax. The x-ray findings showed that "there is no evidence of fluid at this time. (It had been removed as far as possible by chest tap previously.) Following peritoneoscopy, there is a considerable amount of free air in the peritoneal cavity about one inch below each diaphragm. In the subsequent films taken later and on the following day, there was still a considerable amount of air. There is no air in the pleural base or in the mediastinum." In the latter two patients there probably was no opening between the chest and the abdomen. In Case 24 there was a hernia, but it is not probable that this opening was of the pleuroperitoneal type. It is apparent therefore that it is unlikely that abdominal fluid arrives in the chest by way of a "hole" in the diaphragm. It is not possible to rule out groups of small openings that might occur through the muscle bundles and various attachments of the diaphragm. It would seem if such were present that the experiments tried in Cases 25 and 26 would have shown air in the abdomen in one and air in the chest cavity in the other. Such findings were not present.

How then does the fluid find its way into the chest? In two patients (Cases 24 and 25), 2 c.c. of sterile *India ink* was injected in the abdomen, and chest taps performed later. In each instance the fluid in the chest showed the same concentration of *India ink* as in the abdomen. Concentrations were gauged grossly. Microscopic examination showed essentially the same number of carbon granules in the mononuclear cells of each fluid. That the *India ink* did not arrive in the pleural fluid by way of the blood stream was considered established by study of the blood shortly after injection of the abdomen with *India ink*. In the two patients (Case 25, Fig. 1 and Table I), the blood showed no evidence of *India ink* in the leucocytes on microscopic examination. This experiment is suggestive evidence that the abdominal fluid in these

TABLE I. (CASE 25) CARBON INJECTION

Chest fluid:	Mononuclear cells loaded with carbon
Abdominal fluid:	Mononuclear cells loaded with carbon
Blood (Buffy Coat):	No carbon seen

patients arrives in the chest by the same pathway as the India ink, or vice versa. The probability is that the pathways are lymphatics, first through the interstices of the cells under the diaphragm, thence to the supradiaphragmatic lymphatics and thence into the chest.

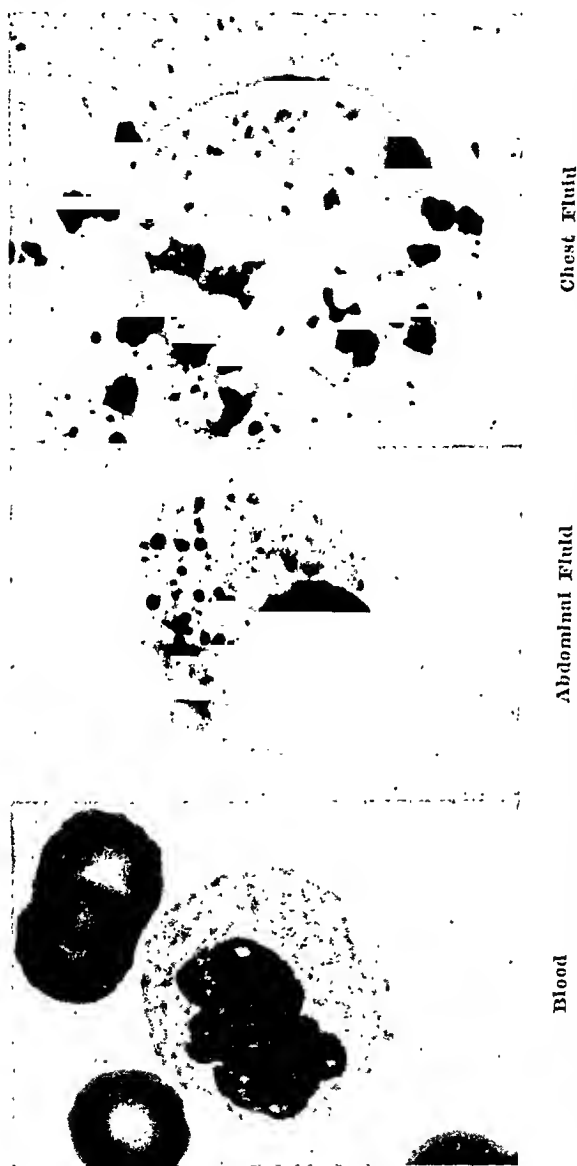


Fig. 1.—Case 24. Microphotographs of mononuclear cells from blood, chest, and abdominal fluids following the preoperative injection of India ink into the abdominal cavity. The cells from both chest and abdomen show phagocytosis of carbon particles; the cells from the blood do not.

Barring differential rates of absorption of components, if the two fluids come one from the other, they should be chemically identical. A comparison of the fluids of the chest and of the abdomen should provide corroborative evidence that the two fluids are in open communication. Fluids, therefore, taken by thoracentesis and from the abdomen at operation were compared as to total protein, and electrophoretic distribution of protein components, namely, albumin, alpha, beta, and gamma globulins, and fibrinogen. Such a comparison in two

patients (Case 24, Fig. 2 and Table II, and Case 25, Table III) shows that the two fluids are indistinguishable within the limits of the method.*

The identity of the fluids with respect to all aspects measured (protein concentration, protein distribution, India ink concentration) makes probable a fairly free communication between the fluids in chest and abdomen.

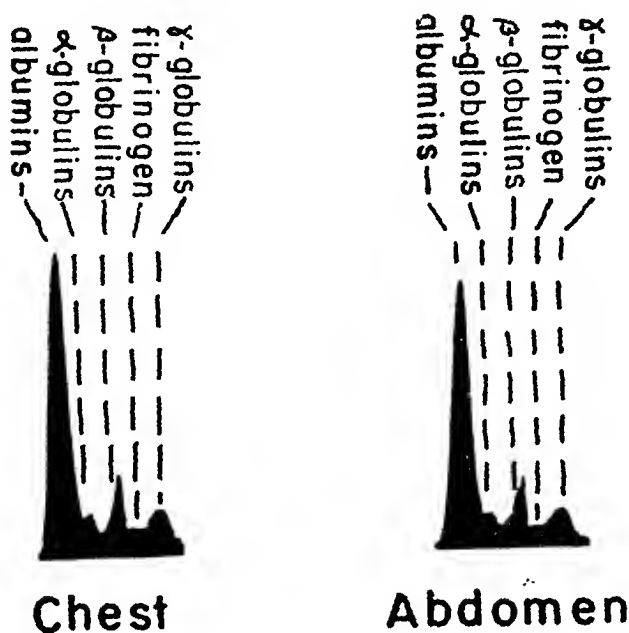


Fig. 2.—Case 24. The area of the skewed probability curve lying below each peak is a measure of the relative concentrations of the protein components noted above the peak. It will be seen that beyond a slight difference in total area (representing a difference in total protein concentrations at which the measurements were made) the patterns are essentially identical.

TABLE II. (CASE 24) ELECTROPHORETIC DISTRIBUTION OF PROTEINS IN CHEST AND ABDOMINAL FLUIDS

TOTAL PROTEIN	ABDOMEN 3.5 GM./%	CHEST 3.7 GM./%
Albumins	73.5%	73%
α -Globulins	5.5%	5%
β -Globulins	13.0%	13%
Fibrinogen	1.0%	2%
γ -Globulins	7.0%	7%

TABLE III. (CASE 25) ELECTROPHORETIC DISTRIBUTION OF PROTEINS IN CHEST AND ABDOMINAL FLUIDS

TOTAL PROTEIN	ABDOMEN 4.7 GM./%	CHEST 4.7 GM./%
Albumins	72.0%	72.0%
α -Globulins	4.5%	4.5%
β -Globulins	11.0%	10.5%
Fibrinogen	3.5%	4.0%
γ -Globulins	9.0%	9.0%

*The divergence between fibrinogen concentrations lies below the limits of accuracy of planimetry in these schlieren diagrams.

TABLE IV. SYNOPSIS OF 27 CASES OF MEIGS'S SYNDROME

CASE AND DATE	AUTHOR	AGE	STA-TUS	CHIL-DREN	CHIEF COMPLAINT	TUMOR	LOCA-TION OF EFFU-SION IN THORAX	THORA-CEN-TESIS	ABDOM-INAL PARA-CEN-TESIS	FLUID AT OPERATION
1. March, 1879	Cullingworth ²⁵	36	M	Yes	Metrorrhagia. Collapse	Bilateral	Left	0	0	Died without operation. Autopsy
2. March, 1891	Tait ^r	36	S	?	Abdominal swelling	Right	Right and left	Repeat-ed	30	Large quantity of ascitic fluid
3. April, 1901	M. G. H. ¹	42	S	None	Pain in right chest	Ovary	Right	4	1	Considerable straw-colored ascitic fluid
4. June, 1902	M. G. H. ¹	55	M	Yes	Pleurisy	Right	Right	5	0	6 to 8 quarts of ascitic fluid
5. Oct., 1908	M. G. H. ¹	38	M	Yes	Pain in shoulder, especially on left	Left	Right and left	7	4	Several quarts of ascitic fluid
6. July, 1917	Hoon ²⁶	36	M	Yes	Bloating of abdomen. Cough. Loss of strength	Ovary	Left	1	0	Marked ascites
7. Nov., 1920	Hoon ²⁶	53	M	None	Bloating. Pain between scapulae	Right	Right	3	1	Several liters of ascitic fluid
8. March, 1926	Leo ²⁷	64	?	?	Dyspnea. Pain in chest	Left	Right	Repeat-ed	0	Large amount of ascitic fluid
9. April, 1928	de Rouville et al. ²⁸	58	M	Yes	Cough. Emaciation	Right	Left	1	9	1,000 c.c. ascitic fluid

10. Sept., 1930	Bonze and Kirsh- baum ²⁹	37	M	Yes	Pain in abdomen. Low- er abdominal mass	Left	Right and left	0	0	Free serous fluid
11. April, 1932	Salmon ²⁴	52	M	?	Abdominal mass. Cramps	Right	Right	3	0	500 c.c. ascitic fluid
12. Aug., 1934	M. G. H. ³⁰	52	S	None	Dyspnea. Change in bowel habits	Left	Right	Repeat- ed	1	Large amount of yellow ascitic fluid
13. July, 1936	Miller ³¹	60	S	None	Pressure. Weakness. Disability	Right	?	3	0	?
14. Aug., 1936	Weld ³²	55	?	?	Swelling of abdomen	Bilat- eral	Right	0	0	3,500 c.c. ascitic fluid
15. Sept., 1936	Weld ³²	50	M	?	Enlargement of abdomen	Right	Right	0	0	Blood-tinged ascitic fluid
16. Jan., 1937	Macomber ³³	33	S	None	Tumor in abdomen. Dyspnea	Left	Right	1	1	Two quarts of ascitic fluid
17. March, 1937	Rhoads and Terrell ³⁴	57	M	Yes	Shortness of breath. Fatigue	Right	Right	5	0	750 c.c. ascitic fluid
18. Nov., 1937	Bonze and Kirsh- baum ²⁹	45	M	?	Lower abdominal mass. Bearing-down sensa- tion. Backache. Ede- ma of feet and ankles. Slight dyspnea. Left thoracic pain	Left	Left	0	0	Free serous fluid
19. July, 1939	Borg ³⁵	44	M	Yes	Pain in abdomen. Short- ness of breath	Bilater- al	Right and left	2	1	Died without operation. Fair degree of ascites at autopsy
20. Aug., 1939	Harris and Meyer ³⁶	67	M	Yes	Shortness of breath. Fatigue	Left	Right	1	1	200 c.c. ascitic fluid

TABLE IV—CONT'D

CASE AND DATE	AUTHOR	AGE	STATUS	CHILDREN	CHIEF COMPLAINT	TUMOR	LOCATION OF EFFUSION IN THORAX	THORACIC CENTESIS	ABDOMINAL PARACENTESIS	FLUID AT OPERATION
21. Dec., 1939	Henderson ³⁷	42	?	?	Breathlessness	Bilateral	Right	4	0	Large amount of ascites
22. March, 1940	Loek and Collins ³⁸	31	M	Yes	Abdominal pain. Distention. Mass in abdomen	Left	Right	0	0	Four liters of clear fluid
23. March, 1941	Glass and Goldsmith ³⁹	73	?	?	Shortness of breath. Swelling of abdomen	Right	Right	1	0	400 c.c. straw-colored fluid
24. April, 1941	Meigs	66	M	None	Pleurisy. Backache. Asthma. Dyspnea	Left	Right	4	1	500 c.c. straw-colored fluid
25. June, 1941	Meigs	51	M	Yes	Cough. Dyspnea	Left	Right	3	0	500 c.c.
26. Dec., 1941	Ritvo ⁴	57	?	?	Pressure in lower abdomen. Prolapse. Slight dyspnea	Right	Right	2	0	Two quarts
27. Nov. 8, 1940	Breen and Nelligan ⁴⁰ (not reported in literature)	23	S	None	Swelling of abdomen. Frequency. Dyspnea	Right	Right	1	0	Large amount of straw-colored fluid

It should be noted that the chemical data alone do not lead to such a conclusion. They merely corroborate the implications of the rapid passage of particulate carbon from abdomen to chest. There is no *a priori* reason why chest and abdominal fluid, elaborated under similar pathologic conditions, whether comprising carcinoma or cardiac decompensation, be not essentially identical chemically. Indeed in a limited number of instances of cardiac insufficiency, simultaneous studies of fluids from peritoneum and pleura have demonstrated identity with respect to total proteins and electrophoretic distribution.¹⁸

It is evident that particulate matter, placed in the abdominal fluid of the two patients herein reported with a fibroma of the ovary and fluid in the chest arrives in some way, probably transdiaphragmatic, in the chest fluid.

The fact that air cannot follow the same route may well be merely an indication of the relatively small size of the communications: such that the pressures here involved were not sufficient to overcome the surface tension phenomena which *in vitro* can obstruct the free flow of air in a wet capillary tube.

The passage of particulate carbon is of considerable interest when considered with relevance to the mechanism of hydrothorax in conjunction with ascites in certain conditions other than Meigs' syndrome. Statistical considerations enhance this interest. For Meigs' syndrome is rare in comparison with ovarian fibromas with ascites alone.* So, likewise, is hydrothorax and ascites rare in comparison with Laennec's cirrhosis with ascites alone. It may be that hydrothorax is found in conjunction with ovarian fibroma or portal hypertension in those few patients who also have sufficient congenital mechanical communication between peritoneum and pleura. Extension of this hypothesis leads to investigation of the possibility of such communication in conditions where the basis of fluid in both cavities is more readily explicable, e.g., cardiac decompensation and metastatic carcinoma.

Initial experiments in this investigation have been completed. In two patients, one with carcinomatosis, the other with Laennec's cirrhosis; particulate carbon injected into the pleural fluid failed to attain the peritoneal fluid within twenty-four hours.

At first glance, this result might be taken to indicate that no communication exists in these instances. However, it should be noted that in two cases of Meigs' syndrome (Cases 24 and 25), only communication from abdomen to chest, not from chest to abdomen, has been demonstrated.

The possibility of a one-way communication is emphasized by the investigations of Lemon¹⁹⁻²¹ and his associates on dogs. These workers found that particulate matter injected in the abdomen of the dog reached the diaphragmatic lymphatics, but particulate matter injected into the chest did not reach the inside of the abdomen.

They placed hydrokollag (a compound of graphite) in the peritoneal cavity of dogs and found the graphite particles in the supradiaphragmatic lymphatics and in the anterior mediastinal lymphatics. India ink as well as hydrokollag apparently penetrated the interstices of the cells of the subdiaphragmatic peritoneum and was picked up by the lymphatics and arrived in the lymphatics of the pleural diaphragm and later those of the mediastinum. Hydrokollag was also found in the retroperitoneal spaces about the spleen and kidneys, arriving there by

*Approximately 75 per cent or more ovarian fibromas are accompanied by ascites.

way of other lymph channels. Experimentally, then certain particulate matter can penetrate the diaphragm, but as experimental animals have no fluid in their chests, the question as to whether or not this material would enter a pleural effusion is not proved but is suggested.

Whether a truly one way communication can exist in man and to what extent the communication may be demonstrated in conditions other than Meigs' syndrome, will be discussed on completion of further studies.

No attempt has been made to include in this paper reports of cystadenomas, fibroids, or cancers with fluid in the chest as well as in the abdomen. A few reported cases are those of W. T. Dannreuther²² whose patient, according to MacFee, ultimately died of cancer; a multilocular cystadenoma reported by MacFee;²³ a fibroid reported by Salmon,²⁴ and one case, mentioned in this paper, which is the only one of this type in *Myomata of the Uterus* by Kelly and Cullen.⁹ There are not many reported as yet, and it is very possible that more will be. When they are, and when they constitute a large enough group, they should be included in the syndrome. It may be found that many benign pelvic tumors and certain malignant tumors without metastases in the chest may give rise to the same picture.

Conclusions

1. Two cases of Meigs' syndrome are reported wherein the fluid in the abdomen and chest were identical with respect to all aspects measured.

2. In these cases particulate carbon passed from abdominal to chest fluid quickly and easily.

3. Three important investigative problems emerge from Meigs's syndrome:

- a. The mechanism whereby ovarian fibromas give rise to abdominal fluid.

- b. The mechanism of the hydrothorax.

- c. The question as to whether similar mechanisms operate in instances of combined hydrothorax and ascites where the primary pathology is other than fibroma of the ovary.

4. Cullen, Kelly, and others, have shown that in lesions other than ovarian fibroma fluid may be present in the abdomen. Whether this fluid is similar to that found in patients with fibromas has not been proved, though it may be considered probable. In most cases of uterine fibroids with fluid there are adhesions of omentum to the tumor or twists of the pedicle which are not present in the fibromas reported here.

5. It remains for joint investigation by thoracic surgeons and others to demonstrate the presence of diaphragmatic perforations of small or large size, the presence of the rarely reported pleuroperitoneal tubes, and

to determine the direction and degree of penetrability of the diaphragmatic lymphatics.

6. The syndrome of ovarian fibroma with hydrothorax and ascites is of practical clinical significance. Further studies on patients thought to have cancer with metastases to the chest should be carried out.

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Discussion

DR. WILLIAM P. HEALY.—The most intriguing aspect of Dr. Meigs' paper is of course the question of how this fluid gets into the pleural cavity. I have had two cases, one benign and the other malignant, and in each instance there was fluid in the pleural cavity, in one case in the left and in the other in the right chest. In

the case with the malignant ovarian tumor there was no extension of the tumor to the chest, which, therefore, makes the problem similar to that of the nonmalignant cases.

My patient of benign ovarian tumor exhibiting this syndrome was on the service of both Mount Sinai Hospital and Memorial Hospital and the correct diagnosis was not made in either institution until I operated upon the patient. The case history of this patient follows:

G. B., a single Jewish woman of 48, was admitted to the Memorial Hospital on Nov. 29, 1931. She had been under observation in Mount Sinai Hospital for several weeks during September and October of that year. The menopause had taken place ten years previously. The present illness had begun with swelling of abdomen four months prior to admission. This was soon accompanied by irregular abdominal pain and after a time, by shortness of breath. About two months previously the family doctor had made a diagnosis of abdominal tumor.

Physical examination disclosed a well-nourished female, who, however, appeared quite ill. There was dullness in the left chest posteriorly and evidence of pleural fluid. The abdomen was greatly distended and one could readily palpate a large, somewhat freely movable, ballotable mass which filled the pelvis and extended somewhat above the level of the umbilicus. The abdominal wall and ankles were somewhat edematous. Vaginal and rectal examinations disclosed no additional information.

A letter of inquiry which was sent to Mount Sinai Hospital elicited the following information: The patient had been in that hospital from Sept. 23 to Oct. 7, 1931. Two thousand cubic centimeters of amber-colored fluid was removed from the left pleural cavity after which x-ray of the chest showed an effusion of moderate size in the lower part of the left chest. The lungs showed no abnormality. No tumor cells were found in the laboratory examination of the pleural fluid.

The abdomen was distended by free fluid and an irregular tumor mass was noted extending from the umbilicus into the pelvis. Laboratory findings showed the following: sedimentation time, 10 minutes; hemoglobin, 66 per cent; blood Wassermann, negative; blood urea, 16. Gastrointestinal x-rays were negative except that the barium enema revealed an extracolonic mass occupying almost the entire left half of the pelvis, reaching to the level of the fourth lumbar vertebra. There was also an indication of another mass in the right half of the pelvis, displacing the colon upward but no intrinsic lesion of the colon.

The patient was considered inoperable and referred to Memorial Hospital for x-ray therapy. The final diagnosis was carcinomatosis peritonei.

When I saw the patient after her admission to the Memorial Hospital I first advised removal of the fluid from the peritoneal cavity so we could make a better examination. We removed 6,500 c.c. of clear, amber-colored fluid from the peritoneal cavity. A study of this fluid was reported as showing large mononuclear leucocytes, but no tumor cells could be identified. Following removal of the fluid I was able to identify two dense, hard tumor masses, on bimanual examination. Both these masses were mobile; one was about the size of a child's football and the other the size of a small orange.

On Dec. 1, 1931, I operated and found two large, readily removable fibromas of the ovary of the sizes noted. There was no evidence of intraperitoneal metastatic disease. A supracervical hysterectomy was done, removing the tumor masses with the uterus.

The pathologic report was: Left ovary absent and replaced by a large encapsulated, nodular tumor measuring 17 by 15 by 9 cm. Capsule pinkish white. On section tumor was, for the most part, a solid mass of glistening white fibrous tissue. Numerous cyst cavities, ranging in size from 1 to 5 cm. in diameter, contained straw-colored fluid. The walls of these cavities were smooth. Smaller tumor was solid

and ivory-colored and was incorporated with the right ovary. Gross Diagnosis: Bilateral edematous fibromas of the ovaries. Microscopic Diagnosis: Moderately cellular ovarian fibroma.

The patient's convalescence was uncomplicated. She was followed in the clinic for three years, during which time she remained in excellent health and was then lost trace of. There was no evidence during the aforementioned period of any recurrence of fluid in the chest or of tumor masses elsewhere.

DR. WILLIAM W. HERRICK.—I believe that cases of the kind described are more numerous than is ordinarily supposed. Last spring, at the Association of American Physicians, Dr. Watson and I reported another. In the discussion several members of the Association cited cases of a similar sort.

One of the most significant clinical features of this syndrome is that the patients are practically always without fever. Hydrothorax of almost any other cause is at one time or another accompanied by fever. A recurring, afebrile hydrothorax, with or without demonstrable ascites, in a woman over 30 years of age, should arouse suspicion of an ovarian fibroma.

Our patient was a woman of 74 years who came to my office because her children thought she did not look well. She was thin, slight of figure and looked her age, but had very sound essential organs. At the first examination there was slight dullness at the base of the right lung which I interpreted as an old organized pleurisy. This view fitted well with some calcified nodes that the fluoroscopic examination revealed at the hilus. In a few weeks she returned with a fully developed right hydrothorax. This was tapped altogether about nine times. The fluid disclosed no evidence of infection on guinea pig inoculation or ordinary examination. I did not make a pelvic examination until we had performed the thoracentesis about three or four times. When I did, it was quite apparent that there was a tumor of the right ovary of appreciable size. It then occurred to me that I was dealing with Meigs' syndrome and I invoked the aid of Dr. Watson who removed the tumors which he will describe.

Our patient has enjoyed good health ever since her operation, without a trace of recurrence of fluid. One of the most remarkable features of such cases is the rapidity with which the fluid in the chest vanishes after removal of the tumors and the fact that it does not recur.

The experimental work of Dr. Meigs is very important. One might think the negative pressure in the thorax a factor in promoting the transfer of material from the peritoneum into the thorax and preventing progress in the reverse direction. There are a great many conditions, such as cirrhosis of the liver with ascites, in which one has a complicating hydrothorax in which a like mechanism may be operative.

Dr. Meigs' experimental study should throw light upon the general relation of hydrothorax to abdominal conditions other than fibroma of the ovary which may be attended by ascites.

I am sure that internists have failed to recognize many cases of ovarian fibroma with hydrothorax and have condemned these women to needless suffering, if not death, with an erroneous diagnosis of malignancy. I think it is high time that the medical man, as well as the gynecologist, became alert to this important and, I believe, not too uncommon condition.

Dr. Watson will describe the pathology found in the case to which I have alluded.

DR. BENJAMIN P. WATSON.—The physical findings in this case were similar to those which Dr. Meigs has described.

Here there is shown the large tumor on the left side and a smaller fibroma on the right. The pedicle was not particularly long and I do not think that it had ever undergone torsion.

This patient had comparatively little aseitic fluid in the abdomen. Fluid accumulated repeatedly in the right pleural cavity, however. She made an absolutely uneventful recovery, although 74 years of age. Operation was done under intravenous sodium pentothal anesthesia.

Over a period of nine years there have been in the Sloane Hospital nine cases of ovarian fibroma. Only two of these showed gross ascites, although some of the others probably had small quantities of fluid in the abdomen. This is the only case of ovarian fibroma in which I found fluid in the chest.

DR. WILLIAM E. STUDDIFORD.—Since Jan. 1, 1932, about 25,000 patients have been cared for on the gynecologic service at Bellevue Hospital. About 20 per cent, or 5,000 of these patients, were found to be suffering from some sort of gynecologic neoplasm. About 12 per cent of these, or 600 of the patients, had tumors arising in the ovary. Among the ovarian tumors there were 14, or 2.5 per cent of fibromas. None of the latter patients exhibited the syndrome which has been described by Dr. Meigs this evening, and in only one instance was the clinical picture very closely similar. It may be of interest to report this case in some detail.

The patient was 36 years old, white, married, para 0, gravida 0, admitted to the Third Medical Division of Bellevue Hospital on June 6, 1942. Her menstrual history was normal and her past medical and surgical histories were irrelevant. The chief complaint was progressive shortness of breath and gnawing pain beneath the right scapula, first noticed a week or ten days before admission.

Examination showed a slightly dyspneic patient who appeared otherwise to be in good health. Physical signs and roentgenologic examination both showed evidence of right pleural effusion. Examination of the abdomen was negative. Pelvic examination showed a round, firm, movable mass, about 10 cm. in diameter, in the area of the left ovary. The other physical findings were normal. The pulse was 110 and the temperature 98.6° F. Examination of the blood and urine proved normal.

During the first week after admission to the hospital the right chest was tapped on five occasions, from 1,100 to 2,000 c.c. of serous fluid being obtained, and each of the specimens were blood tinged. Tubercle bacilli could not be demonstrated in the sediment, either microscopically or by guinea pig inoculation.

Sections of the sediment showed groups of epithelial cells arranged in rosettes or about a central core of stroma. Differential stains failed to show the presence of mucin in these cells. Roentgenologic and bronchoscopic examination of the lungs failed to show any primary neoplasm.

The patient was transferred to the gynecologic service and a laparotomy performed on July 10, resulting in the removal of a fibroma of the left ovary. No intraperitoneal fluid was present and no other abnormal condition was noted in the abdomen.

Following removal of this tumor no improvement took place in the right chest. Pain and dyspnea continued, and although smaller amounts of fluid were obtained, it was believed that this could be explained by the development of adhesions with resultant loculation of the effusion. It must be assumed that the process in the right pleural cavity was entirely independent of the fibroma in the left ovary.

The patient is still under observation and repeated studies have failed to reveal any neoplasm apart from the pleural cavity or any suggestion of tuberculosis. The thoracic surgeons are now considering exploration of the right pleural cavity to determine the exact nature of the disease.

While this case at the onset closely resembled the condition described this evening in its clinical aspects, it can be easily differentiated by the character of the pleural fluid which, on examination, showed not only red blood cells, but peculiar epithelial elements. These findings have never been described in a case of pleural effusion secondary to fibroma of the ovary.

DR. HOWARD C. TAYLOR, JR.—My contribution to this discussion is the report of one additional case of Meigs' syndrome which I treated last May. The patient was quite typical as far as the previous history and course were concerned. She was 72 years of age and gave a history of about three years of abdominal discomfort. Roentgenologic examinations of the gastrointestinal tract had been made by an internist who saw the patient a few minutes after the onset of symptoms. Ten months before coming to me the patient noticed an abdominal tumor and at about the same time fluid was found in the chest. Thereafter she was for sometime considered to be an inoperable case of carcinoma of the ovary. When she finally came to the Memorial Hospital, the lack of progress of what had been regarded as a malignant condition led to the diagnosis of a fibroma of the ovary.

The patient underwent a thoracentesis and about 500 c.c. of fluid were removed. She was studied carefully before operation and the blood count, plasma protein level and other laboratory data were normal. At operation there was disclosed a typical fibroma of the ovary with moderate ascites. The postoperative course was uneventful and examination six months afterward failed to reveal any fluid in the abdomen or thorax.

I would like to ask whether Dr. Meigs has succeeded in dissociating hydrothorax entirely from the ovarian tumor. Is the appearance of fluid in the chest cavity now to be considered in no sense specific for the ovarian tumor but something which is as likely to occur with ascites from any other cause.

DR. JOE VINCENT MEIGS.—I did not mention that this report covers 27 patients and the three added tonight increases the number to 30. Dr. Herrick said that at his meeting in Atlantic City about six or more were mentioned. The total is a considerable number, especially when it is borne in mind that when we started in 1934 there were only three cases. Many are new and many have been reported in the literature.

One of our patients did have fever. She was operated upon by Dr. Harrington. He became so upset about the case that one day he made a large opening in the chest under local anesthesia, and inserted a tube. An infection developed and he said "that is the end of it, now she has laudable pus, she will get well." But, she did not get well until later when the tumor was removed.

I believe Dr. Armstrong thinks that fluid in the abdomen and chest is not at all specific for the ovary. Any abdominal fluid can get into the chest, as for example, in cirrhosis of the liver. If there is a hole or holes, they may be large or even tiny perforations as Dr. Churchill has suggested. It seems to me that the fluid above the diaphragm is due to lymphatic drainage. However, I do not know. The two fluids are identical as has been shown by electrophoretic studies. I do not think that only an ovarian tumor will do it; I think any fluid in the abdomen may do the same thing. Irritation above the liver in a subdiaphragmatic abscess, for example, may cause fluid above the diaphragm. The chief thing in this discussion is that there is such a syndrome. If we can report 30 such cases there must be many more. We saw three cases last year because we are more on the alert and are looking for such cases. The peritoneoscope should help us.

NUTRITION STUDIES DURING PREGNANCY

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I. Problem, Methods of Study and Group Studied

GROWTH begins with conception, not with birth. Growth requires dietary essentials to a greater extent than maintenance. Although in the earliest part of pregnancy the ovum carries some nutrient material within itself, it must necessarily be dependent upon the mother for the major portion of the material from which it is to grow and develop.

The interrelationship of mother and fetus and the extent of dependence of the fetus upon the maternal diet are problems which must be solved before the role of nutrition in pregnancy can be thoroughly understood. These must be studied through observation of the prenatal diet and general health, both of which may be heavily conditioned by the mother's preconceptual state. Stated specifically, a complete study of the effect of nutrition upon fetal growth and development should attempt to determine: (1) the effect of the mother's preconceptual health and nutrition upon the prenatal course and upon the development of the fetus; (2) the nutritional requirements in respect to pregnancy and the relationship of the mother's preconceptual nutritional state to the requirements of pregnancy; (3) the relative importance of the essential nutrients to the course of pregnancy, labor, delivery, the puerperium and to the development of the fetus and the health of the infant.

While numerous papers on prenatal nutrition in relation to fetal development and the health of the infant have been published, only a few illustrations of fetal damage resulting from prenatal nutritional deficiency will be mentioned. An outstanding illustration is the work of the University of Wisconsin Agricultural Experiment Station¹ on the effects of different rations upon growth and reproduction. These workers found that the corn-fed heifers gave birth to full-term vigorous young, normal in size and able to stand and suck within an hour after birth. They all lived and developed normally, whereas the young of the wheat-fed mothers were born prematurely, were small, and either were stillborn or died within a few hours. The young of the mothers who were fed the oat plant ration or a mixture of the three grains were weak or stillborn. The mothers were continued on the experimental

rations and the following year repeated in all the essential details their previous reproduction records. Evidence of damage to the human fetus from inadequate nutrition in the prenatal period is also to be found.²⁻⁴

The metabolic studies of Macy and her co-workers⁵ and of Coons⁶ have added much factual data on the nutritional requirements of women in this period. The recent work of Ebbs, Tisdall and Scott⁷ evaluates the diet of the mother in relation to her condition, as well as to the condition of the infant at birth and during the early months of life. An interim report of the Committee of the People's League of Health in England⁸ gives interesting statistical data on the effects of improvements in prenatal diet by the use of nutritional concentrates.

Material

The material presented in this paper and those to follow originates in data collected on a selected group of mothers and their children over a period of twelve years and is a part of the research program on the growth and development of the well child undertaken by the Department of Child Hygiene of the Harvard School of Public Health. The work was begun in 1930 and the program enlarged to include the establishment of a Center for Research in Child Health and Development.* Three hundred and twenty-four children have been enrolled at the Center, and approximately two hundred of these children are still actively enrolled. A description of the work at the Center is given in another publication.⁹

The women for this study were chosen from the prenatal clinics of the Boston Lying-in Hospital. The observations during pregnancy, labor, delivery, and the puerperium were made in the early years of the study by the obstetricians of the hospital and later by those on the staff of the Center. These women were seen at least monthly through the seventh month of pregnancy and every two weeks during the eighth month and weekly thereafter, unless seen more frequently because of complications.

At the first visit to the prenatal clinic, a thorough physical examination was made and complete medical and obstetric histories obtained. At all subsequent visits, blood pressure and weight were recorded and the urine examined for albumin and sugar. Careful notations were made of any complications of pregnancy and of any intercurrent illnesses. These data have been supplemented throughout the entire series by periodic nutrition histories, certain social, economic, and other information in regard to the patient and her family.⁹ A number of the group in the latter part of the series were included in special studies.^{10, 11} Hemoglobin and hematocrit values have been obtained and will form the basis for a special report.

The obstetrician evaluated the condition of the infant at birth, and always within forty-eight hours a physical examination was made also by a pediatrician from the staff of the Center. These observations were augmented by notes from the hospital records. Infants whose neonatal course was not entirely satisfactory were seen frequently by

*The work of the Center was made possible in part under a grant from the General Education Board of the Rockefeller Foundation. The nutrition studies have been supported in part by a grant from the Forsyth Dental Infirmary for Children, Boston.

a pediatrician from the Center, who also examined each infant before discharge from the hospital, usually on the fourteenth day of life. It is upon these data that the pediatric ratings used in this paper and subsequent papers of the series, describing the condition of the infant at birth and within the first two weeks of life, are based.

The nutrition data used in this study were obtained during the first two years by a woman pediatrician and during the last ten years by a trained nutritionist. Dietary histories were obtained at the mother's first visit to the prenatal clinic and at as many subsequent visits as the individual case necessitated, at least once each trimester. These histories include a complete record of the food intake for the twenty-four-hour period preceding the clinic visit, data about the woman's food habits previous to and during pregnancy, food likes and dislikes, amounts of foods purchased, number of persons in the family, amount of money spent for food each week and other related data. In addition, each woman kept at regular intervals a record of food consumed over a consecutive three-day period, which was compared with the dietary history taken by the nutritionist for that period. The amounts usually eaten daily of such important foods as milk, meat, eggs, whole grain products, vegetables and fruit have been carefully investigated, as well as the amounts of highly refined carbohydrate and fat-rich foods. This was carefully studied to learn to what extent these latter types of foods were replacing foods rich in essential proteins, minerals, and vitamins. Such a method of cross-checking important data contributed greatly to the accuracy of the final dietary estimates. Sample forms used in taking these nutrition histories and further details as to the method employed are given in a monograph published by this Center.⁹

The method used in analyzing these nutrition data is described in detail in another publication.¹² In evaluating the diet for the last two trimesters of pregnancy, a rating for each nutritional essential was assigned, based upon comparison with an arbitrary set of values accepted as "optimal." These arbitrary values are given in Table I. In evaluating the diet for the first trimester of pregnancy and for the period previous to pregnancy, the normal nutritional requirements for the average woman, given also in Table I, were chosen as "optimal." It is observed that they approximate the values recommended by the Food and Nutrition Board of the National Research Council.

TABLE I. OPTIMAL DAILY NUTRITIONAL REQUIREMENTS IN PREGNANCY AND THE OPTIMAL NORMAL REQUIREMENTS OF THE AVERAGE WOMAN*

NUTRITIONAL ESSENTIALS	NORMAL	PREGNANCY† (4TH THROUGH 9TH MONTH)
Calories‡	2,200-2,400	2,600-2,800
Protein, Gm.	60	85-100
Calcium, Gm.	0.8	1.5
Phosphorus, Gm.	1.32	2.0
Iron, Mg.	15	20
Vitamin A, § I.U.	5,000	8,000
Thiamin, Mg.	1.5	2.0
Riboflavin, Mg.	2.0	2.5
Niacin, Mg.	15	18
Ascorbic acid, Mg.	70	100
Vitamin D, I.U.		400-800

*Generally accepted optimal nutritional requirements, according to available data.

†Assuming the changes in the first trimester to be so small as to be negligible.

‡Energy requirements vary with activity, size of the individual, etc.

§The requirement for vitamin A may be less when provided as vitamin A and may be more if provided chiefly in the form of carotene.

An essential nutrient present in the prenatal diet in this "optimal" amount was assigned a rating of "excellent." For example, if the average protein intake from the fourth month of pregnancy amounted to 85 Gm. or more daily, the diet was called "excellent" in protein. When the amount was somewhat less but yet 80 per cent or more of the "optimal" standard, the nutritional essential under consideration has been called "good." It has been called "fair" when 60 to less than 80 per cent of the standard was present. Less than 60 per cent of the "optimal" standard has been called "poor," and if the average intake was under 50 per cent, it has been termed "very poor."

The "mean" general dietary ratings were obtained by assigning a numerical value to each rating, as "very poor" = 0, "poor" = 1, "fair" = 2, "good" = 3, and "excellent" = 4. This has allowed the assignment of a "mean" value to the average dietary intake of each woman during pregnancy and has done much to remove any personal impressions of those analyzing the data in regard to the general adequacy of the diet. It also means that the dietary evaluations are more accurate when used in comparative studies, as their relative relationships to each other are more exact. This made it possible to handle the nutritional data easily and accurately from a statistical standpoint. It should be remembered that owing to the method of deriving the "optimal" nutritional standards (Table I), which involved adding to the accepted minimum requirements a liberal allowance for safety and individual differences in needs, it is possible that a diet rated "fair" may have been at least "good" under certain circumstances.

Observations upon 216 women and their infants will be presented in this paper. In this first series of cases, only the oldest sibling of each family in the study is included. Data on approximately the last 150 cases are derived from a more reliable sampling and represent in each field material more discriminately collected than that on the earlier cases. Group I consists of all cases up to and including Case 150 who were oldest siblings, and Group II, all oldest siblings beyond Case 150. The second group is by necessity somewhat smaller, as the study children beyond Case 150 naturally include many more siblings. Group II also included several women drawn from a special group weighted with cases which had toxemia in previous pregnancies and three women with definite toxemia who had premature infants.* These weightings must be recalled in interpreting the data presented. One hundred and twenty-three cases fall in Group I, and 93 in Group II.

The parents of these infants are largely of Northern European stock, 85.3 per cent in Group I and 92.4 per cent in Group II. From an economic standpoint, the parents were selected to represent the average "middle class" American family with incomes ranging from \$25 to \$40 per week in the majority of the families.

In Group I, 53 per cent of the women were 25 years of age or less, 28 per cent were between 25 and 30 years, and 19 per cent were over 30 years of age at the time of delivery. In Group II, 40 per cent were 25 years or less, 39 per cent were between 25 and 30 years, and 21 per cent were over 30 years of age.

The number of months of prenatal care received by the mothers is presented in Table II, and in Table III the complications of their pregnancies are given.

*One specialist on the staff of the Center was particularly interested in premature infants.

TABLE II. MONTHS OF PRENATAL CARE

NUMBER OF MONTHS	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
3 Mo. or less	35	28.5	9	9.7	44	20.4
3½-4 Mo.	31	25.2	15	16.1	46	21.3
Over 4 Mo.—less than 6 Mo.	27	21.9	19	20.4	46	21.3
6 Mo. or more	30	24.4	50	53.8	80	37.0
Totals	123	100	93	100	216	100

From Table III, it is seen that in each group 40 women had complications during the prenatal period: 32 women had one complication, 6 had two, and 2 had three. Only those women in Group II whose hemoglobin levels were found to be below 60 per cent at one or more examinations are included in this table. Hemoglobins below 75 per cent, however, are considered a definite indication of anemia needing treatment. The women in Group II had hemoglobins done regularly as a part of their routine examinations, but this was not the case in Group I, where no woman was described as anemic, unless the anemia was of such a degree as to have been recognized clinically and then confirmed by the laboratory. The difference in the number of cases of anemia noted in the two groups suggests the desirability for routine hemoglobin determinations during the prenatal period.

TABLE III. COMPLICATIONS OF PREGNANCY

	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%*	NO. CASES	%*	NO. CASES	%*
Pre-eclampsia	17	13.8	11	11.8	28	13.0
Nausea and vomiting, severe	6	4.9	10	10.8	16	7.4
Sepsis:						
(1) Salpingitis	1	0.8			1	0.5
(2) Otitis media	1	0.8			1	0.5
Urinary tract infections	3	2.4	2	2.2	5	2.3
Prenatal staining	9	7.3	7	7.5	16	7.4
Heart disease	3	2.4			3	1.4
Anemia	3	2.4	8	8.6	11	5.1
Miscellaneous†	8	6.5	12	12.9	20	9.3
Total number of complications	51		50		101	
Total number of women with complications	40	32.5	40	43	80	37
Total number of women with uncomplicated pregnancy	83	67.5	53	57	136	63

*The figure in this column gives the percentage incidence of each type of complication in relation to the total number of women in each group.

†The miscellaneous group includes blepharitis, pigmented degeneration retina of eye, duodenal ulcer, syphilis, chronic nephritis, leucorrhea, severe epidermophytosis of hands, severe eczema of face, respiratory infections, hydrannios, edema, desquamation of finger tips, fibroids.

Table IV shows the parity of the women under study. The majority of the women in both groups were primiparas.

In every case labor was spontaneous, with the exception of 7 cases of induced labor and 3 cesarean sections without test of labor. The duration of labor is given in Table V, the type of delivery in Table VI, and the complications of labor and delivery in Table VII.

TABLE IV. PARITY

NUMBER OF PREGNANCY	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
1	80	65.1	66	71.0	146	67.5
2	31	25.2	21	22.6	52	24.1
3	10	8.1	5	5.4	15	6.9
4 to 7	2	1.6	1	1.0	3	1.5
Totals	123	100	93	100	216	100

TABLE V. AVERAGE HOURS OF LABOR*

PARITY	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	AVERAGE NO. HR.	NO. CASES	AVERAGE NO. HR.	NO. CASES	AVERAGE NO. HR.
Primiparas	76	16.6	68†	14.9	144	15.8
Multiparas	43	10.0	18	10.4	61	10.1

*All cesarean sections (11) excluded.

†63 primiparas and 5 essential primiparas.

TABLE VI. TYPE OF DELIVERY

	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
Normal	71*	57.7	41	44.1	112	51.8
Low forceps†	38*	31.0	37	39.8	75	34.7
Midforceps	2*	1.6	3*	3.2	5	2.3
Scanzoni	2‡	1.6	4‡	4.3	6	2.8
Breech extraction	5	4.1	1	1.1	6	2.8
Version extraction	1	0.8	0		1	0.5
Cesarean section	4	3.2	7§	7.5	11	5.1
Totals	123	100	93	100	216	100

*In Group I manual rotation of the head was necessary in one normal, one low forceps and one midforceps case. In Group II one midforceps delivery involved a manual rotation of the head.

†This number of low forceps deliveries should be considered in the light of the policy of the Boston Lying-in Hospital, which provides for delivery by low forceps if the cervix is fully dilated and the head is on the perineum for one hour without progress.

‡In Group I one of the Scanzoni deliveries was also low forceps; the other was midforceps. In Group II all were low forceps.

§One cesarean section was followed by a hysterectomy.

There were no abortions* in this series, but it should be mentioned that almost all of the women in Group I were registered during or following the third month of pregnancy. Data on the termination of the pregnancies studied are given in Table VIII.

Complications during the post-partum period are presented in Table IX.

The distribution of the birth weights of the 216 infants and the distribution of the crown-heel lengths of the infants will be discussed in a subsequent paper.

*The term abortion is used according to the definition of the American Public Health Association: "The term *abortion* should be reserved for the expulsion or extraction of the product of conception previous to its presumed viability, usually understood to apply to a fetus of less than twenty-eight weeks from the assumed date of conception (6½ calendar, or 7 lunar months, at which time, in the races prevailing in the United States, the fetus will weigh 1,500 Gm. or 3¼ pounds and have a length of 35 cm. or 14 inches)."

TABLE VII. COMPLICATIONS OF LABOR AND DELIVERY

	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%*	NO. CASES	%*	NO. CASES	%*
Fetal distress	13	10.6	6	6.5	19	8.8
Excessive blood loss	2	1.6	1	1.1	3	1.4
Placenta previa	2	1.6	2	2.2	4	1.9
Dystocia:						
(1) Primary uterine inertia	4	3.3	3	3.2	7	3.2
(2) Secondary uterine inertia	32	26.0	32	34.4	64	29.6
(3) Disproportion	5	4.1	7	7.5	12	5.5
(4) Malposition	8	6.5	10	10.7	18	8.3
Induction of labor	3	2.4	4	4.3	7	3.2
Retained placenta	1	0.8	1	1.1	2	0.9
Miscellaneous†	6	4.9	11	11.8	17	7.9
Total number of complications	76		77		153	
Total number of women with complications	57	46.3	58	62.4	115	53.2
Total number of women with normal labor and delivery	66	53.7	35	37.6	101	46.8

*The figures in this column give the percentage incidence of each type of complication in relation to the total number of women in each group.

†The miscellaneous group includes prolapsed cord, vaginal laceration, contraction ring, manual extraction, cesarean before term because of preeclampsia, coryza, spontaneous premature rupture of the membranes, separation of old cesarean section scar, and exploration of the uterus.

TABLE VIII. TERMINATION OF PREGNANCY UNDER STUDY

INFANT	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
Full term	117	95.1	83	89.3	200	92.6
Premature	2	1.6	7*	7.5	9	4.2
Stillborn	4	3.3	1	1.1	5	2.3
Died within 2 hours			2	2.1	2	0.9
Totals	123	100	93	100	216	100

*This group contains 3 infants who were enrolled at the request of one of the examining pediatricians because of their prematurity. The prenatal nutrition data on any case of this type were taken by our nutritionist in the post-partum period in the hospital.

II. Relation of Prenatal Nutrition to Condition of Infant at Birth and During First Two Weeks of Life

In considering the effects which prenatal nutrition may have on infant morbidity and mortality, an investigation was made of the relationship between the diet of the mother during pregnancy and the condition of her infant at birth and within the first two weeks of life. Since limitations of space make it impossible to present in this paper the complete data on all of the 216 infants, only the extremes of the groups (that is, the best and the poorest) are presented.* The pediatric ratings of the infants were studied in relation to the mean general dietary rating assigned to the mother's diet during pregnancy.

*It should be remembered in studying the relationships obtained that the ratings used in each field (pediatric, obstetric, nutritional, anthropometric, etc.) have been made independently on all mothers and their infants under study by the specialist in charge of the particular field, and the results in each field assembled to determine possible associations of statistical significance.

TABLE IX. COMPLICATIONS DURING POST-PARTUM PERIOD

	GROUP I		GROUP II		TOTAL GROUP	
	NO. CASES	%*	NO. CASES	%*	NO. CASES	%*
Elevated temperature	16	13.0	12	12.9	28	13.0
Puerperal sepsis	6†	4.9	5	5.4	11	5.1
Phlebitis			2	2.2	2	0.9
Retention of lochia, subinvolution, and retained secundines	20	16.3	9	8.7	29	13.4
Hemorrhage, post partum	1	0.8	4	4.3	5	2.3
Urinary tract infections	8	6.5	9	9.7	17	7.9
Retention of urine	8	6.5	17	18.3	25	11.6
Post-partum pre-eclampsia	6	4.9	6	6.5	12	5.6
Mastitis	2	1.6	3	3.2	5	2.3
Cervical erosion	2	1.6			2	0.9
Anemia	5	4.1	3	3.2	8	3.7
Heart disease	3	2.4			3	1.4
Miscellaneous‡	15	12.3	10	10.7	25	11.6
Total number of complications	92		80		172	
Total number of women with complications	53	43.1	43	46.2	96	44.4
Total number of women with uncomplicated post-partum period	70	56.9	50	53.8	120	55.6

*The figures in this column give the percentage incidence of each type of complication in relation to the total number of women in each group.

†One patient died eleventh day post partum.

‡The miscellaneous group includes shock, bronchial pneumonia, otitis media, other respiratory infections, perineal fistula, pityriasis rosea, hematoma vagina, ileus, drug reaction, ischemic paralysis, fibroids, lymphadenitis and rectovaginal fistula.

All infants in both groups who were considered to be "superior" were selected. The term "superior" means that the infant at birth and during the first two weeks of life was rated by the pediatrician as of "excellent" or "good" condition, with no physical count of any kind recorded against it. As representative of the other extreme of the group all infants were selected who were in the "poorest" condition, that is, were stillborn, died within a few hours or days of life, had a marked congenital malformation at birth, were premature (under 5 pounds at birth), or were "functionally immature." The term "functionally immature" means that the physical development or reactions of the infant were considered below normal in some way and does not apply to weight and length alone. All of the 216 infants not included in the extremes were rated in physical condition somewhere between these two extreme groups.

When the condition of the infants is studied in relation to the mother's mean general dietary rating for the prenatal period, it is found that 56 per cent of the mothers of these infants had had "good" or "excellent" diets, 35 per cent, "fair" diets, while only 9 per cent had had "poor" diets during pregnancy. In contrast, when the condition of the "poorest" infants, i.e., those who were stillborn, etc., is studied in relation to the mother's diet during pregnancy, it is found that 79 per cent of the mothers had diets which were rated as "poor" or "very poor," 18 per cent had "fair" and only 3 per cent had "good" or "excellent" diets during pregnancy. This relationship is shown graphically in Fig. 1.

The average birth weight of the infants considered to be in "superior" physical condition was 8 pounds 2 ounces (range 6 pounds 10 ounces to

11 pounds 7 ounces), and their average birth length* was 20 inches (range 18.5 inches to 21 inches). In contrast, the average birth weight of those infants in the "poorest" physical condition was 5 pounds 15 ounces (range 3 pounds 4 ounces to 8 pounds 15 ounces), and the average birth length was 18.6 inches (range 16 inches to 20.5 inches).

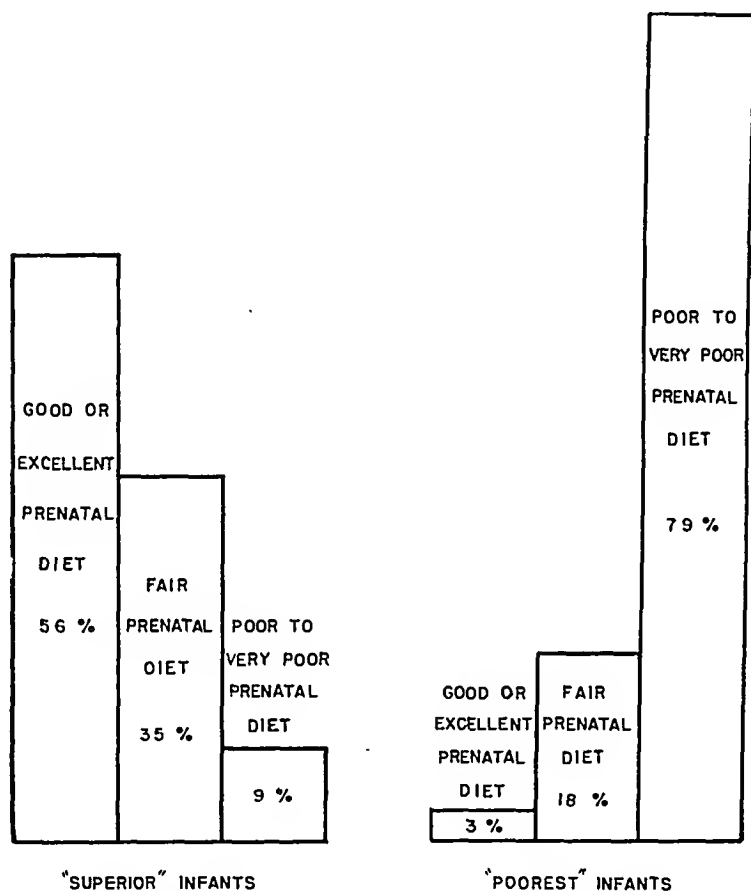


Fig. 1.—Relationship of the condition of the infant at birth and during the first two weeks of life to the mother's diet during pregnancy. (Cases were selected on the basis of pediatric ratings of infants.) "Superior" infants (23): All infants rated at birth and during the first two weeks of life as of "excellent" or "good" condition with no detrimental physical count of any kind. "Poorest" infants (33): All infants who were stillborn or died within a few hours or days (7) (three of these had congenital malformations: multiple anomalies [2], congenital urethral stenosis [1], one died of bronchitis and bronchopneumonia on the 3rd day); infants with marked congenital malformations who lived (9) (malformation of the heart [3] [1 died at 5 months], cleft palate [2], congenital cataracts, premature also [1], congenital mobile funnel chest [1] erythroblastosis mild [1], hydrocephalus arrested, premature also [1]); other premature infants (7); all infants who were "functionally immature" (10).

In order to see if results of equal statistical significance would be obtained, the cases were then selected on the basis of the mother's dietary rating during pregnancy, rather than on the basis of pediatric ratings. All of the 216 cases in which the mean general dietary ratings for the prenatal period were "excellent" or "good" were chosen, and the condition of these infants was studied. When the infants selected on the basis of the mother's dietary rating during pregnancy are studied, it is seen that 42 per cent of the infants whose mothers' diets were rated

*Only measurements made by members of our staff are included.

"good" or "excellent" were "superior" infants, 45 per cent had only one physical count each, though of such minor importance in the majority of cases that the pediatric rating was "good," in other words in almost as good physical condition as those termed "superior," 10 per cent had two minor physical counts each, and one infant (3 per cent) had a congenital defect. In contrast, *all* of the 216 cases in which the dietary ratings for pregnancy were "poor to very poor" were selected and the condition of these infants studied. It was found that 67 per cent of the infants born to mothers whose general dietary ratings were "poor to very poor" were stillborn, died within three days of birth, had

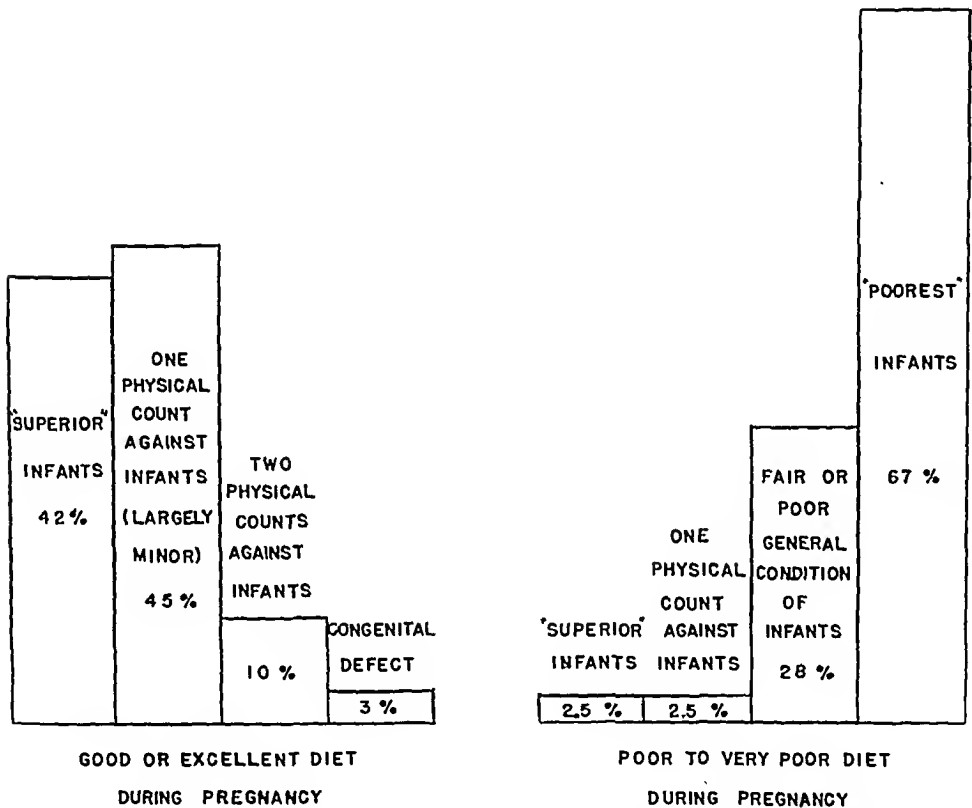


Fig. 2.—Relationship of the mother's diet during pregnancy to the condition of the infant at birth and during the first two weeks of life. (Cases selected on the basis of mother's dietary ratings during pregnancy.) Infants whose mother's diet during pregnancy were "excellent" or "good" (31): "Superior" infants 13 (these are 13 of the 23 "superior" infants shown in Fig. 1); infants with one physical count (largely minor) against each (14), these were small umbilical hernia (4), cephalhematoma (2), subconjunctival hemorrhage (1), conjunctivitis (3), throat infection (1), small hemangioma (1), scalp infection (1), webbed toes (1). Infants with two physical counts (also minor) against each (3): These were receding lower jaw and apathetic (1), conjunctivitis and asphyxia or cyanosis (2). Infant (1) with congenital heart (this infant appears in the "poorest" group in Fig. 1). Infants whose mothers' diet during pregnancy was "poor to very poor" (36): "poorest" infants (24) (these are 24 of the 33 "poorest" infants in Fig. 1), stillborn or died within few hours or days (7) (2 of these had congenital malformations, multiple anomalies [1] and congenital urethral also premature, one died of bronchitis and bronchopneumonia with marked congenital defects who lived (6) (congenital heart s, congenital cataracts, premature also [1]; a mentally retarded mild [1], hydrocephalus, arrested, also premature [1]; cleft palate [1]; a feeble-minded child). Other premature infants (5); infants who were "functionally immature" (6); infants in fair or poor general condition (10) (malnutrition [1], hyperirritability in varying degrees [3], calcaneo valgus deformity and hemangioma [1], strabismus and condition otherwise fair [1], functional maturity fair [3], skin infection [?], thrush and otherwise fair [1]); infant condition good except for small umbilical hernia (1); "superior" infant (1) (this infant is one of the superior infants in Fig. 1).

congenital defects, were premature or "functionally immature," 28 per cent were considered to be in "fair" or "poor" general condition, and only 5 per cent were in "good" or "excellent" condition. These results are shown graphically in Fig. 2. It should be emphasized that practically all the infants born to mothers receiving "good" or "excellent" diets during pregnancy who were not called "superior" had only slight defects, such as mild transient conjunctivitis, small umbilical hernia, small hemangioma, etc. Actually, all but one infant born to these mothers with "good" or "excellent" diets during pregnancy were in "good" condition at birth, while only 2 infants born to mothers with "poor to very poor" diets during pregnancy were in "good" condition at birth.

Likewise, when considering birth weights and lengths of infants selected on the basis of the mother's diet, an average weight of 8 pounds 8 ounces (range 6 pounds 12 ounces to 11 pounds 7 ounces) and an average length of 20.4 inches (range 18.5 inches to 21.5 inches) were found for those infants whose mothers had superior diets during pregnancy. The average birth weight of the infants whose mothers' diets were rated "poor to very poor" was 5 pounds 13 ounces (range 3 pounds 4 ounces to 8 pounds 15 ounces), and the average birth length was 18.6 inches (range 16 inches to 20.75 inches).

The fact that the relationships are similar whether the cases are selected from the standpoint of the condition of the infant or selected on the basis of the rating assigned to the mother's diet during pregnancy makes this relationship which exists between the mother's diet and the condition of her infant of even greater statistical significance. There can be no doubt from these findings that, if the mother's diet during pregnancy is poor to very poor, she will in all probability have a poor infant from the standpoint of physical condition. If the mother has a good or excellent diet, she will probably have an infant in good or excellent condition, but occasionally a mother whose diet in the prenatal period is good will have a poor infant. It is important to note that of the total 216 cases, 132 cases are between the two extremes in both pediatric and dietary ratings, so that the same relationship exists between the condition of these remaining infants in the group and their mothers' nutrition in the prenatal period. This further emphasizes the important relationship existing between prenatal diet and the resulting condition of the infant.

III. The Relation of Prenatal Nutrition to Pregnancy, Labor, Delivery, and the Post-Partum Period

The Course of Pregnancy.—The course of pregnancy was considered normal in 68 per cent of the cases in which the mean general dietary rating for the period of pregnancy was "excellent" or "good"; complications were found in 32 per cent of these cases. Of the cases in which the dietary rating for the prenatal period was "poor to very poor," only 42 per cent of the women experienced a normal prenatal course, while 58 per cent had complications. These relationships are shown graphically in Fig. 3. While there is a statistically significant relationship between the mother's dietary rating and the course of her pregnancy, it is also evident that this relationship is not as marked as that existing between the mother's dietary rating for the period of pregnancy and the condition of her infant. This indicates that with an

inadequate prenatal diet the fetus suffers to a greater degree than the mother. In other words, the fetus is parasitic upon the mother only to a certain extent, and that extent is limited apparently by the mother's nutritional state at the time she enters pregnancy and by the quality and quantity of her diet during pregnancy. It is of utmost importance to realize this fact, because in the usual clinical examination during pregnancy it is not possible to evaluate adequately the condition of the fetus, and it is entirely possible that a woman may have an apparently satisfactory clinical course, but if she is consuming an inadequate diet, the fetus will suffer. Contrary to the usual obstetric teaching, the health of the fetus is greatly dependent on the mother's nutrition during pregnancy.

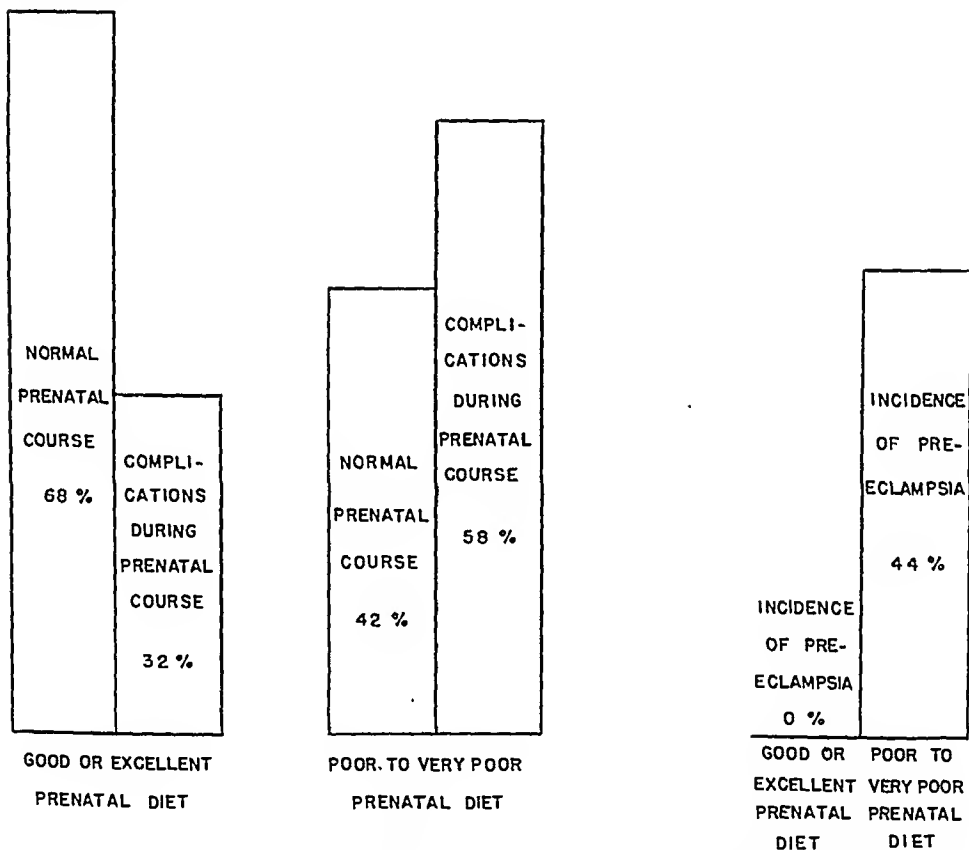


Fig. 3.—Relationship of the prenatal course to the mother's diet during pregnancy. Incidence of pre-eclampsia in relation to the mother's diet during pregnancy. Of the women (31) whose diets during pregnancy were "excellent" or "good," 21 had a normal prenatal course, 10 had complications, such as severe nausea (4), rheumatic heart disease (no failure [1], marked anemia [1]), severe epidermophytosis of hands (1), duodenal ulcer (1), edema (1), staining (1). Of the women (36) whose diets during pregnancy were "poor to very poor" 15 had a normal prenatal course, 21 had complications as follows: pre-eclampsia (16) (nine had other complications as well), pernicious vomiting and severe anemia (1), marked anemia (3), staining (1).

The greater incidence of complications during pregnancy among the women with a "poor to very poor" diet is due largely to a high incidence of pre-eclampsia in this group. While there was no incidence of pre-eclampsia in any pregnancy where the diet was rated either "excellent" or "good," there was an incidence of 44 per cent among the women whose diets during pregnancy were rated "poor to very poor." This is shown graphically in Fig. 3. There was an 8 per cent incidence

of pre-eclampsia in the intermediate group of 132 women. It appears that a significant relationship exists between prenatal nutrition and the incidence of pre-eclampsia in pregnancy. A good or excellent diet during pregnancy would seem to assure its absence, but with a poor to very poor diet during pregnancy, the mother runs an almost 50 per cent chance of having pre-eclampsia.

Labor and Delivery.—The average number of hours of labor of all the primiparas whose diets during pregnancy were rated "good" or "excellent" was 14, and this same figure was obtained for the primiparas whose dietary ratings were "poor to very poor," including the tests of labor made in two cases of cesarean section. If the test hours of labor of these cesarean sections are excluded, the average number of hours of labor of the primiparas of this group was 12. The average number of hours of labor of all multiparas whose diets were rated "excellent" or "good" was 8, while for the multiparas whose dietary ratings during pregnancy were "poor to very poor," the average number of hours of labor was 12. If one considers the types of delivery found in the two diet groups, no cesarean sections had to be performed upon mothers whose diets were "good" or "excellent" during the prenatal period, while 4 cesarean sections were found necessary for women in the "poor to very poor" diet group. There is also a higher percentage of other difficult type deliveries in the "poor to very poor" diet group. This is interesting, since the average birth weight of these infants was markedly lower than that of infants born to mothers whose diets during pregnancy were rated "good" or "excellent." In a consideration of the complications experienced by these women at delivery, only a slightly larger percentage of women, 58 per cent, whose diets during pregnancy were rated "good" or "excellent" experienced a normal delivery than was the case for all women whose diets were rated "poor to very poor"; in the latter group, 50 per cent experienced no complications. If the complications of delivery are classified as *minor* and *major*, it is evident that while the incidence of minor complications was approximately the same in both diet groups, 18 and 14 per cent, respectively, 36 per cent of the "poor to very poor" group had major complications, while in the "good" or "excellent" diet group only 24 per cent had major complications. There was also a greater incidence of fetal distress at delivery among the "poor to very poor" diet group.

It is apparent that any relationship existing between prenatal nutrition and the course of labor and delivery is not clear from this series of cases. The types of labor experienced appear to be more difficult in the "poor to very poor" diet group, despite the fact that the infants born to these mothers were smaller. The incidence of major complications is also higher in the "poor to very poor" diet group. The results from this study do not show a distinct relationship between prenatal nutrition and the character of labor and delivery, as was claimed by Ebbs, Tisdall, and Scott,⁷ nor would we concur entirely in these respects with the findings in the Interim Report of the People's League of Health of England.⁸ These workers reported that they found no appreciable influence of nutrition on the character and duration of labor. It is entirely possible that a relationship may exist between prenatal nutrition and the duration of labor and the character of delivery; if such a relationship exists, we are inclined to believe that it is much less marked than that found with the course of pregnancy, and that many other factors are involved. Among these factors may be the

nutrition of the mother during her own fetal and postnatal development. Because of dietary habits it is probable that persons with poor diets at one period in life would also have had poor diets at earlier periods and that they may belong to families whose dietary habits were poor.

The Post-Partum Period.—When the post-partum course of all mothers whose diets for the period of pregnancy were rated “excellent” or “good” is compared with the puerperium of all women whose diets during pregnancy were rated “poor to very poor,” it is found that an approximately equal number (58 and 56 per cent) of women in each diet group experienced a normal post-partum course. If the complications experienced by these women in the puerperium are separated into *minor* and *major*, it is found that 34 per cent of the women on “excellent” or “good” diets experienced minor complications, and 8 per cent, major complications. With those on the “poor to very poor” prenatal diets, 21 per cent had minor complications, and 23 per cent experienced major complications. The incidence of such major complications as puerperal sepsis is so small in the group studied as to make any conclusions unjustifiable. From the present study, it is evident that while there is a tendency for a relationship to exist between prenatal nutrition and major complications in the post-partum period, there is no distinct relationship such as has been shown with the course of pregnancy.

Conclusions

1. This study has shown a statistically significant relationship between diet of the mother during pregnancy and the condition of her infant at birth.

2. If the diet of the mother during pregnancy is poor to very poor, she will in all probability have a poor infant from the standpoint of physical condition. In the 216 cases studied, every stillborn infant, every infant who died within a few days of birth, with the exception of one, the majority of infants with marked congenital defects, all premature, and all “functionally immature” infants were born to mothers whose diets during pregnancy were very inadequate.

3. If the mother's diet during pregnancy is excellent or good, her infant will probably be in good or excellent physical condition. However, it may happen occasionally (1 out of 216 cases in this series) that a mother whose diet during pregnancy was “excellent” or “good” will give birth to an infant in poor physical condition.

4. A statistically significant relationship was found to exist between prenatal diet and the course of pregnancy. This relationship, however, is not as marked as that existing between the prenatal dietary rating and the condition of the infant. This indicates that when nutrition during pregnancy is inadequate, the fetus suffers to a greater degree than the mother.

5. In this study, no mother whose diet during pregnancy was considered “good” or “excellent” had pre-eclampsia, while with a “poor to very poor” diet during pregnancy, almost 50 per cent had pre-eclampsia.

6. No statistically significant associations were found to exist between prenatal nutrition and the duration and character of labor and delivery.

There was a tendency for the mothers whose diets during pregnancy were "poor to very poor" to have more difficult types of labor and to have more major complications at delivery, despite the fact that these women had, on the average, smaller infants than were born to the women whose diets were "good" or "excellent."

7. No relationships of statistical significance were found to exist between prenatal nutrition and the post-partum course. There seemed to be a tendency toward a relationship between prenatal nutrition and the occurrence of major complications in the puerperium.

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This disease leads to a stunting of bones preformed in cartilage. Bones developing in membranes are but infrequently involved. This condition is to be differentiated from hereditary deforming chondrodysplasia. The latter disease appears early in childhood and is rarely if ever fatal. In achondroplasia, the disturbance is confined to the epiphyseal cartilages, while in the latter the exostoses arise from the diaphyseal side of the epiphyseal line. The condition is rare among Negroes. The condition is hereditary and is inherited according to the Mendelian order. Hydramnios may be an influential factor in the etiology due to increased intrauterine pressure. These patients are always bright or even above average in mental capacity.

All dwarfs are not achondroplasties. In chondroosteodystrophy seen in children and in young adults, the epiphyses appear late and develop slowly. The softening of the bones is due to calcium deficiency. The skull is large but normal, and the vertebrae are flattened. In the female, the pelvic outlet is decreased, while the obturator foramina are enlarged. The bones of the pelvis seem soft and partly decalcified, and x-ray pelvimetry is important if these patients anticipate pregnancy.

WILLIAM BERMAN.

THE RATE OF FILTRATION THROUGH THE CAPILLARY WALLS IN PREGNANCY*

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IT HAS been suggested¹⁻⁶ that one cause of edema in pregnancy, both normal and toxemic, may be increased permeability of the capillary wall, but this has never been clearly demonstrated. This study was undertaken to determine whether the concept of increased capillary permeability in pregnancy could be supported by demonstration of changes in the rate of filtration of fluid through the capillary walls into the tissue spaces. While such deviations from the normal might be to some extent the result of factors other than the state of the capillary wall, none of the other well-recognized causes of edema formation has, as yet, explained adequately the generalized edema of pregnancy.²

The method of measuring rate of filtration was that employing the pressure plethysmograph.^{7, 8} The apparatus and its use have been described elsewhere in detail.⁸⁻¹⁰ Briefly, the volume of a segment of forearm with its blood vessels collapsed was measured repeatedly until a relatively constant value was obtained. Filtration then was effected by raising venous pressure in the forearm, and finally the volume of the segment was remeasured. The actual increase in volume of the segment during ten minutes was converted to cubic centimeters per minute per 100 c.c. of forearm. The volume of the segment of forearm was determined by the geometric method previously described.⁷ All observations were made on the left forearm at 33.5 to 34.0° C. The rest periods between determinations of "reduced arm volume" (tissue volume with blood vessels collapsed) were four minutes, and from 3 to 6 determinations were required to obtain two successive readings differing by less than 1 c.c. The effective venous pressure in the occluding cuff on the upper arm was 50 cm. of water. The actual pressure in the cuff was higher by the amount of a correction factor determined for each observation, thus compensating for the hydrostatic pressure in the vertical forearm (see Landis and Gibbon⁸). The statistical constants were computed by standard formulas, as given by Treloar,¹¹ using corrections for smallness of samples.

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Observations

1. *Normal, Nonpregnant Controls.*—In 12 normal, nonpregnant women, ranging in age from 22 to 35 years, the mean rate of filtration of fluid into the tissues of the forearm was 0.111 ± 0.008 c.c. per minute per 100 c.c. of forearm. The range of individual values was from 0.088 to 0.167 c.c. per minute per 100 c.c. of forearm (Fig. 1, Table I). These values are similar to those found by White and Jones⁹ in 16 normal subjects (9 females, 7 males) with comparable degrees of venous

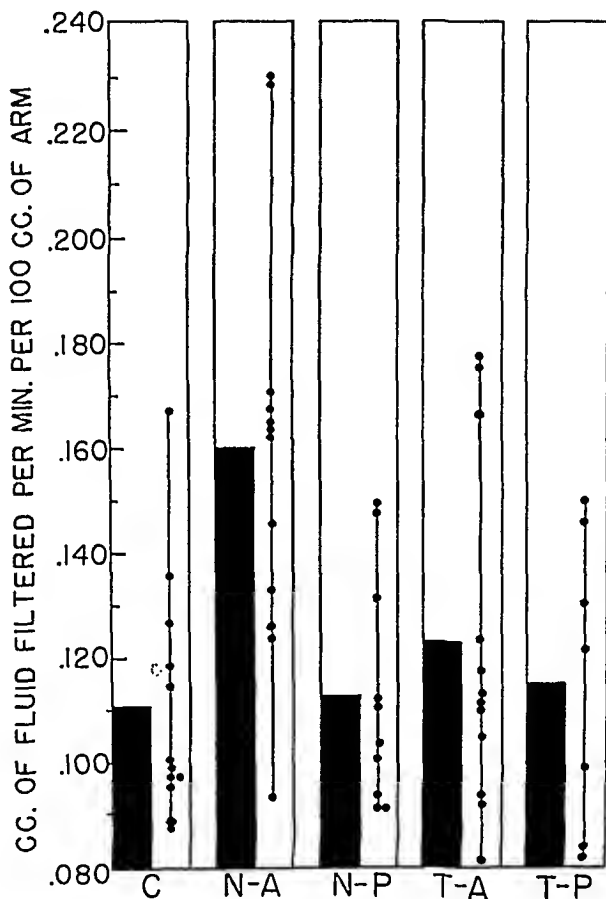


Fig. 1.—Rates of filtration in control subjects (Column C), normal pregnant women (N-A), normal post-partum patients (N-P), toxic pregnancies ante partum (T-A) and post partum (T-P). The solid columns indicate the mean values, the perpendicular lines show the ranges, and the dots on these lines are the individual values.

congestion, and they compare favorably with the few observations of Krogh, Landis and Turner,⁷ and those of Landis and Gibbon⁸ at 50 cm. of venous pressure.

2. *Normally Pregnant Subjects.*—In 12 women observed late in normal gestations (thirty-second to fortieth week), the mean rate of filtration in the forearm was 0.160 ± 0.012 c.c. per minute per 100 c.c. of forearm, and the range was 0.094 to 0.230 c.c. (Fig. 1, Table I). Although many of the individual values for the pregnant women fall within the range of the nonpregnant rates, there is a statistically significant difference between the mean values of the two series (Table III).

TABLE I. RATES OF FILTRATION IN NORMAL WOMEN AND NORMALLY PREGNANT WOMEN AT 34° C.

SUB- JECT	NORMAL WOMEN		NORMALLY PREGNANT, ANTE PARTUM			NORMALLY PREGNANT, POST PARTUM	
	AGE YEARS	FILTRATION RATE C.C. PER MINUTE PER 100 C.C. FOREARM	AGE YEARS	DURATION OF PREG- NANCY WEEKS	FILTRATION RATE C.C. PER MIN. PER 100 C.C. FOREARM	POST- PARTUM DAY	FILTRATION RATE
1	25	0.088	23	40	0.094	-	-
2	27	0.089	21	36	0.124	10	0.104
3	29	0.096	29	39	0.126	10	0.132
4	26	0.098	18	37	0.133	-	-
5	35	0.098	25	37	0.145	70	0.112
6	27	0.099	32	40	0.163	13	0.101
7	26	0.100	25	32	0.164	8	0.092
8	29	0.115	20	40	0.165	13	0.149
9	27	0.119	28	39	0.167	45	0.094
10	22	0.127	30	37	0.171	51	0.092
11	24	0.136	20	39	0.229	13	0.111
12	22	0.167	20	39	0.230	10	0.147
Mean		0.111			0.160		0.113
Standard deviation		0.027			0.040		0.025
Standard error of mean		0.008			0.012		0.008

Ten of the normally pregnant patients were studied after delivery (8 to 70 days), at which time the mean filtration rate had dropped to 0.113 ± 0.008 e.e. per minute per 100 c.e. of forearm. This value does not differ significantly from that of the control subjects, but it is significantly lower than the mean value for the normally pregnant women (Table III).

3. *Pregnant Subjects With Toxemia.*—In 12 pregnant women with clinical diagnoses of pre-eclampsia, low reserve kidney (mild pre-eclampsia), or arteriolosclerotic toxemia, observed in the last six weeks of gestation, the mean filtration rate was 0.123 ± 0.010 e.e. per minute per 100 c.e. of forearm. The range was 0.082 to 0.177 e.e. (Fig. 1, Table II). The average value was not significantly different from that of the control subjects, but it was significantly less than that of the normally pregnant women (Table III).

After delivery (9 to 18 days) 7 of the toxemic women were restudied. At that time the average rate of filtration was 0.116 ± 0.012 e.e. per minute per 100 c.e. of forearm. This was not significantly different from (1) the ante-partum toxemic value, or (2) the rate for the nonpregnant controls, or (3) the post-partum rate for the normally pregnant women (Table III).

Discussion

These observations suggest that fluid filters through the capillary walls more readily in women late in normal pregnancies than it does in nonpregnant women. However, more individuals must be studied at all stages of gestation, with repeated observations in the same subjects, before the evidence will be conclusive. Whether or not the increased rate of filtration in normal pregnancy may be attributed to increased

TABLE II. RATES OF FILTRATION, ARTERIAL BLOOD PRESSURES AND OTHER PERTINENT DATA CONCERNING PATIENTS WITH TOXEMIAS OF PREGNANCY

SUB- JECT	AGE YR.	CLINICAL DIAGNOSIS	HIGHEST ARTERIAL BLOOD PRESSURE MM. HG	LOWEST ARTERIAL BLOOD PRESSURE MM. HG	CLINICAL ESTIMATE OF EDEMA	PLASMA PROTEINS			URINARY ALBUMIN MAX- IMUM	FILTRATION RATE			
						TOTAL GM./100 C.C.	ALBUMIN GM./100 C.C.	GLOBULIN GM./100 C.C.		WK. PREG.	RATE C.C./ MIN./100 C.C. AREA	DAYS P.P.	RATE C.C./MIN. PER 100 C.C. AREA
1	20	Low reserve kidney	136/ 96	120/76	1+	6.5	4.0	2.1	0	40	0.082	-	-
2	21	Pre-eclampsia	152/102	100/60	None	-	-	-	3+	40	0.097	18	0.131
3	20	Pre-eclampsia	180/115	120/80	None	5.5	3.4	1.9	2+	36	0.098	8	0.082
4	20	Pre-eclampsia	150/110	125/80	None	4.7	2.8	1.6	Trace	40	0.105	9	0.150
5	23	Pre-eclampsia	166/115	125/75	1+	5.4	3.2	1.9	Trace	39	0.111	8	0.099
6	35	Low reserve kidney	146/ 95	110/70	1+	6.2	3.3	2.5	1+	41	0.112	-	-
7	23	Pre-eclampsia	150/105	105/70	None	-	-	-	Trace	41	0.113	10	0.084
8	26	Pre-eclampsia	175/110	130/80	1+	6.1	3.7	2.3	1+	35	0.118	9	0.122
9	40	Arteriolosclerotic toxemia	170/125	140/92	1+	5.8	3.8	1.8	Trace	36	0.124	-	-
10	31	Pre-eclampsia	180/120	115/80	None	5.9	3.3	2.3	Trace	32	0.167	9	0.146
11	16	Pre-eclampsia	176/130	114/70	None	5.6	3.8	1.8	1+	35	0.176	-	-
12	17	Pre-eclampsia	156/100	130/80	1+	6.3	3.7	2.6	Trace	40	0.177	-	-
Mean rate of filtration													
Standard deviation													
Standard error of mean													
													0.116
													0.029
													0.012

TABLE III. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN FILTRATION RATES FOR CONTROL, NORMALLY PREGNANT AND TOXEMIA SUBJECTS. RATE OF FILTRATION IN CUBIC CENTIMETERS PER MINUTE PER 100 C.C. OF FOREARM

GROUPS	DIFFERENCE BETWEEN MEANS	S. E. OF DIFF.	R(k) *	P*	SIGNIFI- CANT DIF- FERENCE
Controls vs. normal pregnancy ante partum	0.048	0.014	3.43	0.0006	Yes
Controls vs. normal pregnancy post partum	0.002	0.011	0.18	0.8572	No
Controls vs. toxemic pregnancy ante partum	0.012	0.013	0.94	0.3524	No
Controls vs. toxemic pregnancy post partum	0.005	0.014	0.35	0.7339	No
Normal pregnancy ante partum vs. same, post partum	0.046	0.014	3.19	0.0014	Yes
Normal pregnancy ante partum vs. toxemic pregnancy, ante partum	0.036	0.016	2.31	0.0209	Yes
Normal pregnancy post partum vs. toxemic pregnancy, post partum	0.003	0.014	0.21	0.8330	No
Toxemic pregnancy ante partum vs. toxemic pregnancy post partum	0.007	0.016	0.45	0.6599	No

*R or (k), ratio of difference to its standard error. P, probability of the (k) magnitude being exceeded solely through errors of random sampling.

permeability of the capillary walls cannot, of course, be answered directly by these plethysmographic studies since the colloid osmotic pressure of the blood proteins was not considered in each case in establishing the venous congestion as it was, for example, by White and Jones.⁹ They employed a congesting pressure 20 cm. above the colloid osmotic pressure, as determined from albumin and globulin levels by the formula of Wies and Peters.¹² The reliability of such formulas, however, is open to serious question.^{12, 13} Furthermore, it has been estimated¹ that the average colloid osmotic pressure in normal pregnant women at term is about 28 cm. of water, whereas it was 32 cm. for the normal females in the control series of White and Jones.⁹ If, then, the average congesting pressure in the present series of pregnant women had been 4 or 5 cm. lower to compensate for loss of protein, the rate of filtration would have been somewhat lower, but perhaps not significantly decreased. For example, Krogh, Landis and Turner found that a drop of 1 cm. of water in colloid osmotic pressure was accompanied by an increase in filtration rate ranging from 0.0027 to 0.0045 c.c. per minute per 100 c.c. of arm at temperatures around 28 to 29° C. While normal pregnancy is commonly accompanied by some lowering of plasma proteins, it has not been demonstrated that this is a major factor in the production of edema.^{1, 2} In fact, Dieckmann¹ has pointed out that the greatest diuresis and improvement in edema of pregnancy occurs immediately post partum when the serum protein concentration is lowest.

In view of what is known about filtration into edematous tissues,⁵ and in the light of present concepts of water storage in pregnancy, one would not expect to find an increased rate of filtration in normal pregnancy. The apparent greater ease with which fluid enters the tissues would

suggest a relative state of tissue dehydration. If there be increased permeability of the capillary wall, why is there not sufficient subclinical edema in the latter weeks of pregnancy to diminish the rate of further filtration of fluid? Possibly the stage is set, so far as the condition of the capillary wall is concerned, for the production of edema, but some additional factor is required to establish the edematous state. Could this factor be the hypothetical humoral agent of Weiss²? Unfortunately, these questions cannot be answered by investigations of the present sort.

The diminution in rate of filtration in patients with toxemia of pregnancy could have been predicted from what is known about filtration in the presence of edema.⁸ Apparently, then, even the mildest form of toxemia (see detailed findings in Table II) is accompanied by a considerable degree of edema, although the latter may not be clinically demonstrable even in the lower extremities. All of the toxemia patients were relatively symptom-free at the time of determination of filtration rate although all still exhibited some elevation of arterial blood pressure. Were it possible to study a group of more severely ill subjects, with obvious pitting edema, one might expect considerably lower filtration rates, with subsequent rises in the post-partum period.

Further patients are being studied with a view to confirming the trends indicated here. The subjects must be chosen with some care so that uncooperative individuals will not invalidate the results by moving about during the determinations. It has been impossible to get many pregnant women to remain perfectly still in the supine position for periods of one to two hours. And this fact, as well as certain other considerations, makes it difficult to carry out such tedious physiologic observations on patients with severe degrees of pre-eclampsia or eclampsia.

Summary

Using the pressure plethysmograph at 34° C., the rate of movement of fluid through the capillary wall was studied with a congesting venous pressure of 50 cm. of water in the forearms of 12 normal women, 12 normally pregnant women near term, and 12 pregnant women near term with some form of toxemia. Seventeen of the pregnant patients also were studied post partum.

The mean rate of filtration for the normal controls was 0.111 ± 0.008 c.c. per minute per 100 c.c. of forearm. In the normally pregnant women it was significantly greater, being 0.160 ± 0.012 c.c. After delivery the rate dropped to the control level. The patients with toxemia had a mean rate of 0.123 ± 0.010 c.c. per minute per 100 c.c. of forearm, which was not statistically different from that of the controls, but significantly lower than that of the normally pregnant women. There was no appreciable change in the toxemic patients after delivery.

Conclusions

From observations in a small series of patients, it appears that the rate of filtration through the capillary wall, contrary to expectation, is somewhat increased over the normal in the latter weeks of pregnancy. This may be the result of an increase in the permeability of the capillary wall, although other factors must be considered, particularly the level of the colloid osmotic pressure and the state of tissue hydration. Patients with even mild toxemias of pregnancy appear to have sufficient edema (usually not clinically demonstrable) to interfere with filtration of fluid into the tissues. Toxemic patients with massive generalized edema might be expected to show marked diminution in the rate of filtration.

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The author cites several cases in which saturated saline solution was introduced into the amniotic fluid to initiate active labor at full term. In cases of fetal death, 40 to 80 c.c. were injected. If the fetus was viable, 20 to 40 c.c. were used. The interval between this procedure and initiation of active labor was from forty-five minutes to twenty-four hours. The author feels from results in this short series that the sodium ion has a stimulating effect on the myometrium, and perhaps the increased tension due to added fluid volume in the amniotic sac had a favorable effect in starting labor. In the discussion, mention was made of 2 cases of uterine tetany, which had followed the Aburel procedure in a series of 30 cases observed in Argentina.

R. J. WEISSMAN.

A REPORT ON SEQUENTIAL ABORTION*

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THE causes and treatment of sequential abortion are an important problem in the general consideration of sterility. Approximately 18 per cent of all pregnancies end in miscarriage. When we add to this list the fetal deaths due to abnormalities, prematurity, etc., the fetal mortality is appallingly high. Therefore, this field of obstetrics probably offers the greatest opportunity for fetal salvage of any of the angles of preventive obstetrics. Present-day obstetric care is more inadequate in this respect than the routine prenatal and delivery problems that arise daily. This inadequacy is due to the inherent gaps in our knowledge of the mechanics of implantation of the fertilized ovum, the normal maintenance of growth, and the controlling factors in uterine quietude or expulsive uterine contractions. One method of approach to these clinical problems is the gradual addition to the literature by many observers of careful clinical records so that eventually sufficient material will be available for worth while conclusions.

Material

This report consists of the records of 28 such representative cases, the treatment they received, results obtained, and the impressions gained during their care. No definite conclusions can be drawn, but suggestions for further study may be indicated. As Table I indicates, only 31 completed their pregnancies and three as yet are undelivered gestations. These form the basis of our observations. However, an analysis of the 37 additional pregnancies which these 28 patients had had before they came under our observation, reveal essential details for the evaluation of the whole. In spite of the fact that 12 of these women came primarily for the treatment of long-continued periods of sterility, the sum total of 71 pregnancies is an index of average fertility

TABLE I

Total number of patients	28
Total number of pregnancies	71
Total number of pregnancies treated	31
Total number of pregnancies undelivered	3
Total number of term living babies	16
Total number of pregnancies lost	12
Total number of patients with previous sterility	12
One previous miscarriage	12
Two previous miscarriages	4
Three previous miscarriages	1
Four previous miscarriages	1

*Read at a Joint Meeting of the Chicago, St. Louis, and Kansas City Gynecological and Obstetrical Societies, in Chicago, Illinois, February 21, 1942.

of approximately 2 pregnancies per patient. One might reasonably expect that the factors of disturbed physiology operating in sterility might be responsible for an increased incidence of miscarriage or premature labor, especially since the sterility of 5 of these patients followed a previous miscarriage. In a large series of relatively sterile patients the recurrent factors causing abortion, as described by Malpas,¹ would probably be more frequent than in normal patients. Seventy-five per cent of these patients treated for sterility produced normal, living babies. Twelve of these patients had had 1 miscarriage and 4 of them had had 2. One patient had lost 3 pregnancies and 1 had lost 4.

Malpas has calculated that one out of each 100 patients will abort the second time due to recurrent or random causes, and that this equation will become almost constant after the third abortion. According to his calculations, after the third abortion, only about 27 out of each 100 pregnancies will produce living babies. In this series there were only three demonstrable abnormal factors as listed by this author, one multiple pregnancy, twins delivered at five months, and two fetal malformations. These malformations both occurred in babies delivered during the latter portion of the third trimester of pregnancy. No malformations were noted in the fetuses of the early pregnancies, although they undoubtedly occurred as has been shown by Heusser and Streeter² and many others. In most instances the fetal sac had been discarded by the patient before entering the hospital or no gross evidence of the fetus was found when curettage was performed. There was no evidence of the toxemias of pregnancy or nephritis in these women. All serologic tests were normal, and there were no severe degrees of anemia. These abortions all occurred in private patients of the better class so that dietary deficiencies and environmental factors should have been minimal. Additions of large quantities of vitamins, especially vitamin E, were given early in pregnancy in every case.

The term in weeks or months at which these 71 pregnancies terminated raises questions as yet unanswered.

TABLE II

<i>Term of Pregnancies in Months</i>											
MONTHS	2	2½	3	4	5	6	7	8	9	UNDELIVERED	TOTAL
No. Pts.	9	5	11		3	6		5	29	3	71
<i>Early Abortions in Weeks</i>											
WEEKS	7	8	9	10	11	12	13	14	TOTAL		
No. Pts.	1	8	2	3	2	6		3	25		
Total number of pregnancies delivering between 5 and 8 months										14	
Total number of pregnancies delivering at term										29	
Total number of pregnancies delivering between 7 and 14 weeks										25	

It would seem, as has been previously observed many times, that spontaneous abortion is most likely to occur about the time when a menstrual period would have otherwise occurred. Rhythmic activity such as that causing the menstrual period would seem to be closely related. Hormonal determinations have indicated that decreased production of progesterin may be responsible for sequential abortion. These investigations have also suggested that the production of progesterin is taken over from the ovary by the placenta at about the fourth month

of gestation. We should therefore logically be able to stop progestin substitution therapy at the end of sixteen weeks of pregnancy. In this series of patients only three of the miscarriages occurred between the end of the third and beginning of the fifth month. On the other hand there were three premature labors at five months, 6 at six months, and 5 during the eighth month of gestation. Premature labors would indicate either increased irritability of, or tension in, the uterus or some fundamental weakness of the membranes themselves. Only 29 of the 68 already delivered patients reached full term. It is hard to reconcile the occurrence of two missed abortions, one at six months, with the above facts, except on the basis of random factors.

According to more recently suggested standards, dosage was often quite inadequate. This was especially true in the earlier cases treated. However, a few of these patients paid more for their medication than they did for either their hospital care or medical attention. The average course of treatment and dosage is shown below.

TABLE III. RESULTS IN PATIENTS WITH PREVIOUS STERILITY

1. 11 years sterility	Term living baby
2. 13 months sterility	Term living baby
3. 14 months sterility	5-month premature ruptured membranes
4. 4 years sterility	Term living baby
5. 9½ years sterility	Term living baby. Second pregnancy, 6 months premature
6. 20 months sterility	8 weeks miscarriage
7. 2 years sterility	8 months malformation. Death 10 hours
8. 14 years sterility	7 months premature separation placenta
9. 15 months sterility	Full-term living baby
10. 4 years sterility	Full-term living baby
11. 10 years sterility	Full-term living baby
12. 4 years sterility	Full-term living baby

TOTAL NUMBER OF PATIENTS TREATED WITH			
PROLUTON	PROLUTON AND PROGESTEROL OR PRANON	PRANON	PROGESTEROL
19	4	2	6

FETAL RESULTS IN VARIOUS GROUPS TREATED WITH			
PROLUTON		PROLUTON WITH PRANON OR PROGESTEROL	
LIVING BABY	FETAL DEATH	LIVING BABY	FETAL DEATH
15 (1—L, 1—U)	6 (2—*, 1—O)	3 (1—L)	3

PROGESTEROL		PRANON	
LIVING BABY	FETAL DEATH	LIVING BABY	FETAL DEATH
1	3	1	1

*Fetal malformations. Born alive.

O, Missed abortion.

L, Delivered full-term after this report was completed.

U, Undelivered but near term.

It would seem from the above results if progestin is of help in the treatment of sequential abortion hypodermic administration is to be preferred. The number of patients treated by medication given orally or in combination with injection is too small to comment upon except that they were very disappointing.

A résumé of the case histories is appended.

Abortion Case Histories

CASE 1.—R. L., 1937, aged 41 years. Last menstrual period, May 25, 1939. Previous miscarriage, 12 weeks. Eleven years' sterility. First examination, June 30, 1939. *Pelvic Findings*: Uterus slightly enlarged. Zondek plus, July 3. *Medication*: Thyroid gr. $\frac{1}{2}$ daily, wheat germ oil min. 20 b.i.d.; proluton 5 mg. twice weekly. Bed rest. *Bleeding* began July 21. During next two months 3 periods of bleeding, as much or more than a menstrual period. *Treatment*: Each time by proluton ampoules, one 5 mg. b.i.d. *Delivered*: February 10, 1940. Weight of infant, 6 pounds 7½ ounces.

CASE 2.—B. L., aged 20 years, 10 months' sterility. Last menstrual period, Oct. 21, 1939. Treated 13 additional months for sterility. Aborted 3½ months. No treatment. *Treatment*: for sterility began again Nov. 7, 1938. Thyroid gr. 1 daily until six months, wheat germ oil min. 20 b.i.d., complete bed rest. Proluton 5 mg. twice weekly. Slight bleeding Jan. 4, 1940. Proluton 10 mg. twice daily for 4 days, then 1 mg. daily five days. *Delivered*: July 20, 1940. Weight of infant 9 pounds 6 ounces. This patient is now in the eighth month of another pregnancy. False labor of eight hours' duration occurred at twenty-eight weeks. Given proluton 10 mg.

CASE 3.—H. P. F., aged 31 years. Last menstrual period Aug. 26, 1939. Previous miscarriages; first husband, twins at 5 months; second husband, at three months. *Treatment*: Thyroid gr. $\frac{1}{2}$ daily, wheat germ oil min. 20 b.i.d. Bed rest. Proluton ampoule 1, 1 mg. twice weekly. Two periods of bleeding October 4 to 8, and October 26 to 29. Proluton ampoule 1, 10 mg. b.i.d. during bleeding and for three days after cessation. *Delivered*: Cesarean section June 9, 1940. Weight of infant 6 pounds 5 ounces. Last menstrual period July 23, 1941. Slight bleeding three days beginning Sept. 4. *Treatment*: Progesterol 5 mg. t.i.d. for six days and then 1 daily for seven days. Bed rest. Felt life Nov. 18, 1941. Pregnancy progressing normally.

CASE 4.—E. M., aged 28 years. Last menstrual period May 11, 1940. Previous miscarriages: 1938: 10 weeks term. Two previous full-term pregnancies, last being July 1, 1934. Slight bleeding January 8 and 9. *Treatment*: Proluton ampoule 1, 1 mg. daily, then twice weekly. Bleeding 7 days beginning July 5, 1940. Proluton ampoule 1, 1 mg. daily, wheat germ oil 20 min. b.i.d. Bed rest. *Delivered*: Jan. 30, 1941. Weight of infant 7 pounds 10 ounces.

CASE 5.—B. C., aged 25 years. Last menstrual period Feb. 9, 1941. Previous miscarriage: One 11 weeks from term 6 months ago. Term pregnancies: one 2 years old. Moderate bleeding began April 7, 1941, lasted 7 days. *Treatment*: Progesterol 5 mg. t.i.d. for three days, 2 mg. daily for three days. Progesterol 1 mg. daily, for three days. Bleeding began again April 15, 1941, and above routine repeated. Bleeding stopped April 18. Bed rest, wheat germ oil min. 20 b.i.d. Thyroid gr. $\frac{1}{2}$ daily. *Delivered*: Oct. 24, 1941. Weight of infant 6 pounds 8 ounces.

CASE 6.—Mrs. J. W. M., aged 34 years. Last menstrual period June 1, 1939. Miscarriages, 2. One 10 years ago at 11 weeks term. One 1 year ago at 9 weeks term. Examined first July 28, 1939. *Treatment*: Placed on proluton 5 gr. t.i.d., thyroid gr. $\frac{1}{2}$ b.i.d., wheat germ oil min. 20, b.i.d., relative bed rest. Began bleeding moderately Aug. 7, 1941. Proluton 5 mg. 1 ampoule t.i.d. for three days. Bleeding ceased in forty-eight hours. Proluton ampoule one, 5 mg. continued for 7 days. Bleeding recurred and above routine repeated. Bed rest, continued thyroid, wheat germ oil. *Delivered*: March 12, 1940. Weight of infant 7 pounds 8 ounces.

CASE 7.—C. G., aged 36 years. Miscarriages, one 8 weeks term. No treatment. Last menstrual period approximately March 26, 1938. Bleeding began June 26, 1938, quite profuse. *Treatment*: Proluton ampoule one, 5 mg. t.i.d. for four days. Bleeding ceased in 3 days. Proluton ampoule 2, 5 mg. for two days and then once each day for 1 week. Bed rest, wheat germ oil min. 20 b.i.d. Thyroid gr. $\frac{1}{2}$ daily. *Delivered*: Dec. 26, 1938. Weight of baby 8 pounds.

CASE 8.—D. H., aged 39 years. Miscarriage, one. Nine-week term. No treatment. Previous pregnancy: one normal child, Dec. 29, 1930. Second, 1931 by cesarean section. Ectopic vesicle, repair. Survival. 7 pounds 4 ounces. Last menstrual period Aug. 24, 1939. Bleeding began Nov. 6, 1939. *Treatment*: Proluton ampoule 1, 5 mg. t.i.d. for three days. Bleeding decreased. Ampoule 2, 5 mg. b.i.d. two days. Brownish discharge 9 days. Proluton 1 ampoule 5 mg. daily 12 days. Bed rest. Thyroid gr. $\frac{1}{2}$ b.i.d., wheat germ oil min. 20, b.i.d. *Delivered*: May 14, 1940. Nasal septum absent, cleft palate, brain one-half normal size. Subepicardial hemorrhage, horseshoe kidney. Marked cyanosis after delivery. Death in six hours.

CASE 9.—L. H., aged 33 years. Miscarriages, 2. One 4 years ago, 3 mo. term. One miscarriage 7 years ago, $3\frac{1}{2}$ mo. term. Treated 13 months for sterility. Last menstrual period Feb. 12, 1940. Examined first on March 12. Zondek plus on March 15. *Treatment*: Complete bed rest. Thyroid gr. $\frac{1}{2}$ daily. Proluton ampoule of 1 mg. twice daily. First bleeding slight, on April 10, 1939. Proluton ampoule 1, 5 mg. b.i.d. for 3 days, then ampoule 1, 1 mg. daily for 7 days, followed by ampoule of 1 mg. twice daily. Spotting again May 5. Slight bleeding June 13, 1940. *Delivered*: Aborted June 18, 1940. Infant not weighed.

CASE 10.—K. D. Miscarriages, 3. Two at 6 months and 1 at $5\frac{1}{2}$ months, 1934. Last menstrual period Feb. 27, 1938. Basal metabolic rate minus 14 per cent. *Treatment*: Thyroid gr. $\frac{1}{2}$ b.i.d. Proluton ampoule 1, 1 mg. one to two times weekly. Wheat germ oil min. 15 b.i.d. Continued until thirty-sixth week. Absolute bed rest. *Delivered*: Nov. 20, 1938. Weight of infant 8 pounds 1 ounce.

CASE 11.—M. B., aged 38 years. Miscarriages 2. In 1933 full term, normal; 1937 miscarriage at 2 months, also 1938 at 2 months. Treatment for sterility included removal of cervical polyp at 6 months. Last menstrual period May 1, 1940. *Treatment*: Bed rest, thyroid gr. $\frac{1}{2}$ daily. Wheat germ oil min. 20 b.i.d. Proluton ampoule 1, 5 mg. twice weekly. *Delivered*: Dec. 24, 1940. Weight of infant 5 pounds 6 ounces. Complete atresia second portion duodenum. Lived 10 hours.

CASE 12.—E. H. Normal pregnancy, Dec. 24, 1935. Miscarriages, 4. First, June 25, 1937, at three months term. Second, Jan. 18, 1938, at 10 weeks term. Third pregnancy, last menstrual period, May 20, 1941. Vaginal bleeding began July 10, 1941. *Treatment*: Bed rest. Thyroid gr. $\frac{1}{2}$. Proluton ampoule 1, 5 mg. b.i.d. Pranon 5 mg. daily. Bleeding stopped. Began July 28, 1941. Proluton ampoule 1, 5 mg. daily. Pranon 5 mg. b.i.d. Aborted July 31, 1941. Fourth miscarriage. Last menstrual period Sept. 22, 1941. Zondek positive November 6, 1941. *Treatment*: Complete bed rest. Thyroid gr. 1 daily. Proluton 5 mg. daily. Spotting began Nov. 27, 1941. Proluton 5 mg. b.i.d. Progesterol 5 mg. t.i.d. Aborted Dec. 17, 1941. She is again pregnant and due to deliver Dec. 19, 1942. Proluton 10 mg. daily given from 5 to 30 weeks of gestation.

Cases With One Miscarriage

CASE 13.—G. F., aged 30 years, 1 miscarriage, 2 years three months ago. One full-term pregnancy; child now 4 years old. Last menstrual period July 24, 1939. First seen Sept. 8, 1939. Bleeding slight November 13, 14, and 15. *Treatment*:

Proluton ampoule of 1 mg. daily, for 5 days, then each 2 days for 5 days. Bed rest. Thyroid gr. $\frac{1}{2}$ daily. Remainder of pregnancy uneventful. *Delivered:* April 24, 1940. Weight of infant 9 pounds 2 ounces.

CASE 14.—V. D., aged 29 years. First pregnancy; last menstrual period Jan. 30, 1939. Spotting March 3. *Treatment:* Proluton ampoule 1, 1 mg. daily for 3 days, ampoule 1 each 3 days for 7 days. Thyroid gr. 1 daily. Basal metabolic rate minus 20. *Delivered:* Nov. 13, 1939. Weight of infant 6 pounds 8 ounces. Second pregnancy; last menstrual period Nov. 18, 1940. Zondek positive, Jan. 8, 1941. Bleeding began February 15, 16, and 17, 1941. *Treatment:* Proluton ampoule 1, 1 mg. b.i.d. for 4 days, then ampoule 1 daily for 3 days, then ampoule 1 each 2 days for 5 days. Examined March 28, 1941. Uterus only 7 to 8 weeks size. Missed abortion.

CASE 15.—S. G., aged 28 years. One miscarriage at 4 weeks, 1936. Last menstrual period Jan. 28, 1940. Moderate bleeding began March 18, 1940. *Treatment:* Bed rest. Thyroid gr. 1 daily. Pranon 5 mg. b.i.d. Bleeding and pranon continued for 10 days. Pranon gradually reduced to 1 each 3 days until March 24. Continued until June 4, 1940. *Delivered:* Nov. 3, 1940. Weight of infant 7 pounds 11 ounces.

CASE 16.—H. B., 1 pregnancy, 3 years ago. Present pregnancy: last menstrual period June 22, 1939. Bleeding August 4, 5, and 6. *Treatment:* Wheat germ oil min. 20, b.i.d. Bed rest. Thyroid gr. $\frac{1}{2}$ daily. Proluton ampoule 1, mg. 5 for 3 days, then ampoule 1, mg. 1 daily for 3 days. Bleeding September 5 and 6. Above treatment repeated. *Delivered:* March 23, 1940. Weight of infant 7 pounds 11 ounces.

CASE 17.—H. K., aged 29 years, 1 miscarriage of 8 weeks, Nov. 14, 1939. Last menstrual period Jan. 31, 1940. Examined first April 1, 1940. Uterus 8 weeks size. *Treatment:* Proluton ampoule 1, mg. 1 daily. Bed rest. Thyroid gr. $\frac{1}{2}$ daily. Wheat germ oil min. 20 b.i.d. Bleeding began profusely April 16, 17, 18, 1940. Proluton 5 mg. b.i.d. for 5 days, then 1 each day for 3 days, then 1 ampoule 1 mg. daily. Continued to fifth month. Pranon 5 mg. 3 times a week to sixth month. *Delivered:* Oct. 25, 1940. Weight of infant 5 pounds 1 ounce.

CASE 18.—H. T. One full-term pregnancy; delivered Aug. 25, 1933. Last miscarriage Nov. 8, 1935 at 8 weeks term. Last menstrual period June 7, 1936. Patient fell one-half floor in elevator Jan. 19, 1937. Pains began Feb. 4, 1937. Bleeding irregular until March 11, 1937. Pains began again. Nothing stopped pains except proluton ampoule 1, 1 mg. t.i.d. A similar period of pains of 12 hours' duration on March 15, 1937. *Treatment:* Proluton ampoule 1, 1 mg. every 4 hours. Pains ceased. *Delivered:* March 21, 1937. Weight of infant 8 pounds.

CASE 19.—M. H., aged 39 years, $9\frac{1}{2}$ years' sterility. Treated 2 years. Full-term delivery Dec. 8, 1937. Birth weight 7 pounds 11 ounces. One 6 months premature. Proluton 10 mg. given daily for 1 week preceding premature delivery due to very painful uterine contractions.

CASE 20.—A. K., 10 months' retained fetus. Uterus stopped growing at about 4 months. Curettement advised June 5, 1938. Curetted July 14, 1938. No fetus. Sclerotic placental tissue. Patient, aged 24 years. Last menstrual period April 25, 1939. Moderate bleeding. June 20, 21, and 22. *Treatment:* Proluton ampoule 1, 5 mg. b.i.d. for 5 days. Ampoule 1, 5 mg. daily for 3 days. Ampoule 1, 1 mg. each 2 days until feeling fetal life Sept. 12. Bed rest. Thyroid gr. 1 daily. Wheat germ oil min. 22 b.i.d. *Delivered:* Jan. 26, 1940. Weight of infant 6 pounds 1 ounce. Patient had 4 somewhat profuse but normal menstrual periods beginning late in April. Entered hospital during fifth menstrual period after first week of very

profuse bleeding. During the following 16 days the patient was curetted twice and packed once for profuse bleeding. Hemoglobin and red count were 40 per cent and 2,800,000. Seven thousand seven hundred cubic centimeters of blood were given during this time. Vaginal hysterectomy Nov. 23, 1940. No evidence fetal tissue or other abnormalities on microscopic examination of tissue taken from many areas in the uterine wall. Large vacuoles found in intimal cells of large blood vessels.

Sterility

CASE 21.—D. B., married 11 years. Never pregnant. Treated 15 months. Last menstrual period June 2, 1940. Zondek positive July 19, 1940. *Treatment:* Bed rest. Thyroid gr. $\frac{1}{2}$ b.i.d. Wheat germ oil, min. 20 b.i.d., pranon 5 mg. each 2 days begun August 8. Bleeding began August 14, 15, and 16. Proluton ampoule 1, 5 mg. b.i.d. for 5 days then ampoule 1, mg. 1 each 3 days until Nov. 8, 1940. *Delivered:* March 22, 1941. Weight of infant 6 pounds 10 ounces.

CASE 22.—H. S., aged 36 years. Married 14 years. Treated $3\frac{1}{2}$ years. Last menstrual period May 3, 1941. Bloody discharge began July 3, 1941. *Treatment:* Given progesterol daily. Bleeding continued 2 weeks. One week later progesterol 3 times each week. Felt life Oct. 14, 1941. Rupture membranes, short cord, separation placenta during labor. *Delivered:* Jan. 2, 1942. Infant not weighed. Lived 6 hours.

CASE 23.—E. A., aged 34 years, 20 months sterility treated for 6 months. Zondek positive Dec. 29, 1941. Last menstrual period Nov. 23, 1941. Begun bleeding Dec. 24, 1941. *Treatment:* Bed rest. Thyroid gr. $\frac{1}{2}$ b.i.d. Wheat germ oil 20 min. b.i.d. Progesterol 5 mg. t.i.d. Bleeding lasted $1\frac{1}{2}$ weeks. Progesterol cut to 2 each day. Began spotting again Jan. 19, 1942. Bleeding began Jan. 24, 1942. Curetted Jan. 29, 1942. She is now in her eighth month of pregnancy. Bleeding began $3\frac{1}{2}$ months for 4 days. Proluton 10 mg. daily given.

CASE 24.—C. S. One full term 4 years. One miscarriage. Last menstrual period Aug. 4, 1940. Bleeding began Nov. 8, 1940. *Treatment:* Progesterol 5 mg. 3 times daily. Bed rest. Wheat germ oil. Proluton 1 mg. twice each week. Two doses. *Aborted:* Nov. 11, 1940. Last menstrual period Dec. 6, 1941. Bleeding of 3 days' duration slight, Jan. 3, 1942. *Treatment:* Bed rest. Zondek positive Jan. 5, 1942. Relative bed rest. Pranon 5 mg. daily. Slight bleeding Feb. 7, 1942. Cramps. Proluton 10 mg. daily. Vitamins E and C. Bed rest. Progressing normally. Felt life March 27, 1942.

CASE 25.—V. W., aged 35 years, 8 months delivery May 2, 1937. Erythroblastosis. Last menstrual period June 20, 1935. Bleeding August 14 to 19. *Treatment:* Proluton ampule 1, 1 unit daily for 8 days, then ampoule 1, 1 unit twice each week. Thyroid gr. $\frac{1}{2}$ daily. Bed rest. Bleeding began again Dec. 20, 1935. Proluton ampoule 1, 1 unit each 2 days. Bed rest until March 22, 1936. *Delivered:* March 22, 1936. Weight of infant 7 pounds 2 ounces.

CASE 26.—W. J. L. Child 4 years ago. Living and well. Child 2 years ago. Died intrauterine, retained 10 days in uterus. Last menstrual period Dec. 3, 1938. Felt life April 19, 1939. June 12 no motion, no heart tones. *Delivered:* Aug. 2, 1939. Basal metabolic rate minus 8. *Treatment:* Thyroid 1 gr. daily. Wheat germ 20 drops daily. Last menstrual period May 20, 1940. Above continued. Pranon 5 mg., 3 times each week. *Delivered:* Dec. 25, 1940.

CASE 27.—L. C., aged 23 years. No previous pregnancies. Married 16 months. Mitral stenosis. Last menstrual period Nov. 16, 1941. Bleeding began Jan. 12,

1942. *Treatment*: Progesterol 5 min. 3 times daily. Bed rest. Wheat germ oil min. 20 daily. Bleeding began Jan. 19, 1942. Curetted on Jan. 20, 1942.

CASE 28.—C. H., aged 32 years. Two full-term pregnancies. Last menstrual period Aug. 8, 1941. Spotting began Nov. 3, 1941. Seen first Nov. 10, 1941. *Treatment*: Bed rest, thyroid gr. $\frac{1}{2}$ b.i.d. Wheat germ oil min. 20 daily. Proluton 1 ampoule 5 mg. given in office. Progesterol 5 mg. 3 times daily. Bleeding stopped Nov. 18, 1941. Pregnancy continuing normally.

Summary

Average treatment: Complete bed rest during active bleeding or, as soon as pregnancy was diagnosed in the patient of prolonged sterility, or who had had previous miscarriage.

Continued bed rest for 2 weeks or occasionally to 10 weeks.

Thyroid grain $\frac{1}{2}$ to 1 daily.

Wheat germ oil min. 20, or ethynl acetate 3 mg. each day.

Proluton 1 to 10 mg. 1 to 2 times each day during bleeding, and decreased to 1 mg. twice each week.

Pranon 5 to 10 mg. each day during active bleeding, decreased to each two days.

Progesterol 5 to 10 mg. each day.

No definite conclusion can be drawn from this small group of patients. However, certain impressions may be gained.

1. If progesterone therapy is of value in habitual abortion, it should be extended to the period of viability.

2. That late premature rupture of the membranes suggests estrone predominance.

3. That larger doses of progesterone be used and the preferable route of administration seems to be parenterally.

In the group delivering between the fifth and the eighth month the following fetal conditions were found.

1. One with absence of nasal septum, cleft palate, horseshoe kidney, and small brain.

2. One with complete atresia of second portion of duodenum.

3. One with probable erythroblastosis.

4. Three with premature rupture of the membranes.

5. Two missed abortions, one at five months and another at two months.

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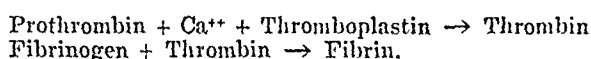
THE FLUIDITY OF MENSTRUAL BLOOD, A PROTEOLYTIC EFFECT*

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ALTHOUGH the presence of fluid blood in the menstrual discharge of normal women has long been known, the subject has not been examined until recently with modern coagulation methods.

It is generally agreed that the coagulation of blood occurs because of the interaction of two proteins, thrombin and fibrinogen. A working mechanism of coagulation, accepted by many investigators, may be summarized as follows:



During menstruation the peripheral blood coagulates normally.²⁻⁴ The menstrual fluid does not contain fibrinogen,^{1, 2, 6, 8} thrombin,^{1, 2, 6, 7} prothrombin,^{1, 2} or anticoagulants.^{1, 2} The calcium content has been stated to be normal^{2, 3, 6} and the fluid contains an abundance of the factor which promotes clotting of hemophilic blood.²

The theory is not new that menstrual blood is fluid because of a lytic agent which dissolves the clot after it has formed in the uterine glands or cavity. Halban and Frankl⁴ found that strips of mucosa in the premenstrual stage digest protein; this proteolytic ferment is absent in the postmenstrual stage. Frankl and Aschner⁵ found that premenstrual uterine epithelium liberated important amounts of tyrosin crystals on incubation with peptone (seidenpepton) in a weakly alkaline solution. Rona and Waldbauer¹² observed that nonprotein N and amino-N of menstrual blood from the uterus were higher than in circulating blood, attributing the increase to proteolysis. Glueck and Mirsky,¹ and Lozner, Taylor and Taylor² concluded that menstrual fluid contains blood which has previously been clotted, the clot being dissolved by some hypothetical lytic agent. Whitehouse⁸ obtained evidence for what he considered to be a specific fibrinolysin: mixing menstrual blood with venous blood in equal amounts, complete resolution of the clot occurred in from twelve to twenty-four hours in 12 cases, with partial resolution in 6 tests. Kross¹⁰ mixed fluid from the uterus of rats with venous blood and observed that the blood clots were dissolved within a short time. He¹¹ also found that hematocolpos fluid from a young woman readily liquefied clots from venous blood in three hours.

Materials and Methods

Menstrual fluid was obtained on the first or second day of catamenia from 38 women by the use of a rubber vaginal diaphragm. The blood

*This investigation was supported by a grant from the Committee for Research in Problems of Sex, the National Research Council.

was collected for three to six hours and tested immediately; in most cases a pinch of sulfathiazole powder (about 50 mg.) was placed in the cup to inhibit bacterial action. Peripheral blood was obtained from the patient, other persons and rabbits; potassium oxalate, 20 mg., was used as an antieoagulant for blood, 10 c.c. and the plasma was diluted 1:4 with saline. Testing for fibrinolysis was carried out by mixing the diluted oxalated plasma, 1 c.c., with menstrual blood 0.5 c.c., either undiluted or diluted with saline to this amount and adding calcium chloride (0.25 per cent), 0.25 c.c. In specified instances no calcium was added. The tubes were placed in a water bath at 37° C. and the time of clotting and of lysis were noted.

In 12 rats under ether anesthesia, the uterine cornua were ligated with silk. Stillbestrol, 0.1 mg. dissolved in olive oil, was injected twice weekly and after two weeks the abdomen was reopened and the uterine secretion aspirated.

Purified fibrinogen, thrombin, and thromboplastin were prepared from beef plasma and lung by the method of Smith, Warner, and Brinkhous²⁰ and prothrombin by the technique of Seegers and colleagues.²¹

Trypsin was determined by the method of Anson¹⁶ and the results were expressed in units of Kolm, Shay and Gershon-Cohen:¹⁷ one unit of trypsin representing the liberation of chromogen equivalent to that produced by trypsin, 1 mg. in one minute per 100 c.c., under stated conditions from denatured hemoglobin. Citrate determinations were made by the method of Pueher, Sherman, and Vickery.¹⁸ Acid and alkaline phosphatase were determined by the King and Armstrong method.^{19, 23}

Results

Clotting Time and Fibrinolysis With Menstrual Fluid.—Determination was made of the coagulation time of 19 specimens of recalcified oxalated peripheral blood, 1 c.c., mixed with menstrual fluid, 0.5 c.c. The clotting time was the same as the controls in four instances, slightly lessened in 12, and slightly prolonged in 3 cases. The most rapid clotting occurred in two and one-half minutes, and the most prolonged time was twelve minutes; the average clotting time of controls in which saline replaced menstrual blood was six minutes.

The effect of menstrual blood on subsequent lysis of the clot is shown in Tables I and II.

Fibrinogenolysis.—The destruction of plasma fibrinogen by menstrual blood was slight. The effect was determined in 12 cases by incubating menstrual fluid, 0.5 c.c., with oxalated peripheral blood, 1 c.c., without additional calcium for two to six hours when calcium chloride was added. All specimens clotted on adding calcium ions in nearly the same time as did the control plasmas containing menstrual fluid where calcium was added immediately after mixing.

Spontaneous Induction of Clotting.—In two tests of twelve, menstrual blood, 0.5 c.c., within one hour caused clotting of oxalated human plasma without added calcium; smaller amounts were ineffective. In the remaining instances, the plasma remained fluid for two to six hours when clotting occurred on adding calcium.

Menstrual blood, 0.5 c.c., always clotted oxalated rabbit plasma, 1 c.c., within one to fifteen minutes without adding calcium. In eight tests, menstrual blood did not induce clotting with less than 0.5 c.c. amounts; in one instance 0.1 c.c. was effective and in one test as little menstrual blood as 0.012 c.c. caused clotting in twelve hours. Spontaneous clot-

TABLE I. FIBRINOLYSIS OF HUMAN OXALATED PLASMA BY MENSTRUAL FLUID

Plasma, 0.2 c.c. + saline 0.8 c.c. + menstrual fluid, 0.5 c.c. either undiluted or diluted to 0.5 c.c. + CaCl ₂ 0.25%, 0.25 c.c.	
Incubation at 37° C.	Dissolution in 18 hours or less
Number of tests: 38	
Complete dissolution	25
Partial dissolution	11
No dissolution	2
Time of solution of clots.	
½—2 hours	11
2—5 hours	6
5—18 hours	8
Amount of menstrual blood causing dissolution: 19 tests.	
No less than 0.5 c.c.	1
No less than 0.1 c.c.	4
No less than 0.05 c.c.	8
No less than 0.05 c.c.	6

ting did not occur in the control rabbit plasmas with saline replacing menstrual blood. Added anticoagulant, potassium oxalate, 8 mg. in 1 c.c. of plasma did not inhibit the clotting effect of menstrual blood.

Dialysis of menstrual blood in a cellulose bag for two days against running tap water still permitted it to induce spontaneous clotting of rabbit plasma. Menstrual blood, 0.5 c.c. did not clot purified beef fibrinogen; after incubation for three hours the addition of thrombin produced quick firm clots. Menstrual blood did not cause clotting of beef plasma from which prothrombin had been adsorbed by colloid Mg (OH)₂.

The Content of Trypsin and the Phosphatases in Menstrual Blood.—Trypsin was determined on 19 menstrual fluids by the method of Anson¹⁶ using denatured hemoglobin as substrate and the results were expressed in the units of Kolm and others.¹⁷ In two cases no trypsin was demonstrated; in seventeen determinations the results ranged from 0.1 to 1.6 units per 100 e.e. The average was 0.63 units.

The trypsin content of rat uterine fluid varied from 0.25 to 1.5 units, the median value was 0.4 units.

Acid phosphatase values in eight tests ranged from 20 to 55.5 King and Armstrong units per 100 e.e. of whole blood; alkaline phosphatases varied from 6.75 units to 23 units. The phosphatases of peripheral blood were not abnormal.²³

Proteolytic Capacity of Rat, Rabbit, and Dog Uterine Fluid.—The uterine fluid of the rat rapidly lysed human blood (Table II); in six tests, plasma, 1 e.e., was completely lysed in one-half to three hours by amounts as low as 0.002 e.e. Human plasma was lysed more effectively and quicker than rat plasma.

Rabbit uterine fluid added in equal parts to human blood produced only slight lysis in eighteen hours.

The uterine fluid of dogs prolonged the clotting times of human and dog blood and exhibited no lytic action in any concentration in eighteen hours. Thirty-one tests were made on uterine fluid of five dogs; fresh blood without anticoagulants, was added to equal volumes of undiluted uterine fluid. The clotting time varied from fifteen to forty minutes. When saline replaced uterine fluid, the average clotting time of human blood was six minutes and of dog blood, three minutes.

TABLE II. EFFECT OF MENSTRUAL FLUID AND UTERINE SECRETIONS OF ANIMALS ON FIBRINOLYSIS OF HUMAN PLASMA
 Oxalated plasma, 0.2 c.c. + saline 0.8 c.c. + secretion, 0.5 c.c., undiluted or diluted with saline + CaCl_2 (0.25%) 0.25 c.c.
 Time of lysis in hours

NATURE OF FLUID	AMOUNT OF SECRETION IN TEST*						
	0.5	0.1	0.05	0.025	0.016	0.0125	
Menstrual fluid	L 1 hour	L 3 hours	L 5 hours	L 18 hours	I 18 hours	0 18 hours	
Menstrual fluid	L 1 hour	L 1 hour	L 4 hours	L 4 hours	I 8 hours	0 18 hours	
Uterine secretion, rat	L 1/2 hour	L 1/2 hour	L 1/2 hour	L 1/2 hour	L 1/2 hour	L 1/2 hour	
Uterine secretion, rabbit	I 18 hours	0 18 hours	0 18 hours	0 18 hours	—	—	
Uterine secretion, dog	0 18 hours	0 18 hours	0 18 hours	0 18 hours	—	—	
Prostatic fluid, man†	—	L 18 hours	L 18 hours	L 18 hours	L 18 hours	L 18 hours	
Prostatic fluid, dog‡	—	L 7 hours	L 18 hours	0 18 hours	0 18 hours	—	

*L, complete lysis; I, partial lysis; 0, no lysis.

†Data of Huggins and Neal.¹³

‡Data of Huggins and Vail.¹³

Lytic Activity of Endometrium.—Saline extracts of endometrium ground with sand were tested against equal volumes of blood. The tissue was obtained from uteri at hysterectomy (Table III). As controls, ground fresh prostate gland from 12 men and thyroid glands from 5 persons were used. Only in the larger concentrations was lysis observed, and excepting one case, there was less lytic activity in endometrial extracts than in the controls.

TABLE III. LYTIC ACTIVITY OF SALINE EXTRACTS OF ENDOMETRIUM AND OTHER TISSUES ON WHOLE BLOOD

TISSUE 1 GM. GROUND WITH SAND IN SALINE, 3 C.C., AND EXTRACTED 24 HOURS AT 4° C.

TEST: HUMAN VENOUS BLOOD, 1 C.C., + 1 C.C. OF SALINE EXTRACT, UNDILUTED OR DILUTED TO 1 C.C.

EXTENT OF LYSIS AT 18 HOURS

TISSUE	AMOUNT OF EXTRACTION IN TEST* C.C.					DIAGNOSIS
	1	0.2	0.1	0.05	0.03	
Endometrium	L	0	0	0	0	Multiple leiomyomas. Residual chronic salpingitis. Hemorrhagic follicles of ovary
Endometrium	L	L	L	0	0	Multiple leiomyomas of corpus. Simple cyst of right ovary. Minute par-ovarian cysts
Endometrium	L	I	0	0	0	Normal corpus and cervix. Multiple follicle cysts of ovary
Endometrium	L	0	0	0	0	Normal uterus. Fallopian tube normal. Bilateral hemorrhagic cysts
Endometrium	L	I	0	0	0	Normal corpus and cervix. Mild salpingitis. Probable luteoma of ovary
Prostate	L	L	I	0	0	Benign hypertrophy
Prostate	L	L	L	0	0	Benign hypertrophy
Prostate	L	L	0	0	0	Benign hypertrophy
Prostate	L	L	0	0	0	Benign hypertrophy
Prostate	L	L	0	0	0	Benign hypertrophy
Thyroid	L	L	L	0	0	Hyperthyroidism
Thyroid	L	L	I	0	0	Hyperthyroidism
Thyroid	0	0	0	0	0	Hyperthyroidism

*L, complete lysis; I, incomplete lysis; 0, no lysis.

Citrate Content of Human Uterine Blood.—The secretion of the human prostate is so rich in citric acid that it prevents the coagulation of blood.¹³ In 6 cases, menstrual blood was tested for citrate; the values were between 1.1 and 5 mg. of citric acid per 100 c.c. Normal peripheral venous blood of 24 adults contained 0.9 to 2.6 mg. per cent.

Discussion

Proteolytic activity as determined by the dissolution of fibrin was observed in 36 of 38 menstrual fluids tested. Fibrinolysis was always greater in specimens collected for a short time and promptly tested than in older samples. All fresh specimens of menstrual blood exhibited fibrinolytic activity which was absent only in those cases where putrefaction had occurred.

The proteolytic activity of menstrual blood against fibrin is weaker than the secretions of the adult prostate gland of dog and man, which in the latter case is particularly strong (Table II). Our observations on the uterine fluid of rats confirm the findings of Kross¹⁰ that strong fibrinolytic activity is present in rat uterine fluid; there is less proteolytic activity in menstrual fluid than in the rat secretion. The rat fluid was opalescent and without obvious signs of infection and did not readily undergo putrefaction, while menstrual blood despite the addition of sulfathiazole tended to spoil. It is of interest that the trypsin content of the exceedingly active rat secretion was no higher by the method used than the trypsin of menstrual blood.

Concerning the relatively mild action of menstrual blood in dissolving fibrin the possibility of the presence of bacterial action which has weakened the protease should be stated. Moreover, it should be stressed that frequently menstrual blood from normal women contains small clots of blood⁸ and is incompletely lysed. Further, there is much evidence that the proteases must be considered as "enzyme + inhibitor" systems;²² it is possible that inhibitors accumulate following lysis of blood depressing further proteolytic activity.

The menstrual fluid resembles prostatic secretion of the dog, and also pancreatic trypsin^{13, 15} in many of its proteolytic characteristics. All of these materials dissolve human fibrin; they induce clotting of oxalated rabbit plasma but not the coagulation of purified fibrinogen or prothrombin-free plasma. Canine prostatic fluid differs from menstrual blood in being very active in destroying fibrinogen, an effect which is slight or absent in the menstrual discharge. Trypsin likewise was demonstrable in nearly all of the specimens examined. No differences were observed between a weak solution of trypsin and the menstrual blood.

The results of this investigation lead to the opinion that the menstrual fluid contains liquid blood because it has been previously clotted and the clot has undergone solution. This view is consonant with previous evidence^{1, 2, 4, 5, 8} and supports the proteolytic theory of menstrual fluidity.

Conclusions

Fresh human menstrual fluid contains proteases capable of dissolving clots of peripheral blood. This activity is considerably less than occurs in human prostatic fluid or semen; it does not disappear on dialysis and does not destroy plasma fibrinogen. The menstrual fluid does not clot purified fibrinogen but constantly clots oxalated rabbit plasma and occasionally clots human plasma without added calcium ion.

Human menstrual fluid contains small amounts of trypsin as measured by its ability to digest denatured hemoglobin. The proteolytic activity of the menstrual blood is physiologically identical with trypsin.

Rat uterine fluid is more actively fibrinolytic than menstrual blood. This uterine secretion does not digest fibrinogen. The fibrinolytic activity of rabbit uterine fluid is slight. Uterine secretion of the dog does not destroy fibrin; it prolongs the clotting of whole blood, whereas rat secretion and menstrual blood accelerate it slightly.

Acid and alkaline phosphatases values of menstrual blood are moderately increased compared to those values in peripheral blood. The citrate content of menstrual fluid is the same as or slightly higher than peripheral blood.

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Keller, R., and Adrian, J.: *Molar Degeneration in Etiology of Early Abortion*, *Gynéc. et obst.* 38: 332, 1938.

Histologic examination of early ovular remains revealed to R. Keller and J. Adrian (Low Rhine Maternity) the great frequency of molar degeneration. They decided to determine whether such molar changes might not be the cause of many unexplained abortions in the early months of pregnancy. Among 305 curettements for incomplete abortion they found fresh villi in only 96 cases, among which were 21 with molar degeneration. In five cases, all the villi had undergone degeneration, whereas in 16 only part of the villi manifested degenerative changes. Hence 21 specimens among 305 (6.8 per cent) showed molar alterations. This is in striking contrast to the statement usually made that a mole is found only once in 2,000 to 3,000 pregnancies. The authors are convinced that a molar change is responsible for many abortions in the early months of pregnancy. Whereas the diagnosis of molar change may be made with the naked eye in a few cases, histologic study is necessary to prove this point in most cases. Hence all tissue obtained at miscarriages should be examined microscopically as a routine. This procedure is particularly important in view of the possibility that a chorionepithelioma may follow a hydatid mole.

J. P. GREENHILL.

HYPOTHYROIDISM AS A PROBLEM IN WOMEN

A Second Report

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THE abnormal development of the thyroid gland presents many interesting problems. Until recent years thyroid hypertrophy and toxic goiter received most attention while hypothyroidism was more or less ignored. Following the advice of Marine, in 1917, I began in 1920 to administer iodine in some form to every pregnant woman who showed any evidence of thyroid hypertrophy which, at first, included 41 per cent of my obstetric patients. Further experience convinced me that all women living in goiter areas should have iodine during pregnancy. Prevention of thyroid hypertrophy was the object of this treatment for it was not then appreciated that the iodine might be of importance in aiding the intrauterine development of a more normal thyroid in the infant.

A review of the data included in my 1926 paper entitled "Thyroid Hypertrophy and Pregnancy"¹ indicates that hyperthyroidism was then a more frequent complication than hypothyroidism although three of the 35 patients on whom basal metabolic rate studies were made had rather low rates. I had observed myxedema and knew that it might follow pregnancy. A number of my sterility patients had evidence of hypothyroidism, and a few cretins had been found in Milwaukee, but it was not then suspected that a considerable group of my patients might be hypothyroid cases. In 1927, while developing a program for the section on obstetrics, gynecology, and abdominal surgery of the A. M. A., I requested a paper on the subject of Hypothyroidism in Women from a large clinic, where many thyroid operations were performed each year, and was informed that they had no data for such a paper.

Preparatory to starting a more or less routine determination of the basal metabolic rate in the examination of my office patients, a survey was made of the findings on all females tested in the laboratory at Columbia Hospital, Milwaukee, for a ten-year period ending Dec. 31, 1931. The records of 1,205 women and girls who had been checked on one or more occasions were reviewed. It was found that 410, or 34 per cent, were above plus ten; within the normal limits were 505, or 42 per cent; while 290, or 24 per cent, were below minus 10 per cent. The lower of the two readings made each time was used rather than an average reading. The patients whom I had sent to the laboratory for basal metabolic rate determinations were checked, with the following results: In a total of 172 females tested there were 34 or 19.8

¹Presented at a meeting of the Philadelphia Obstetrical Society, January 7, 1932. The first report on this subject appeared in the *JOURNAL*, October, 1935.

per cent with a basal metabolic rate above plus ten, 91, or 52.9 per cent, within normal limits and 47, or 27.3 per cent, below minus ten. This review convinced me that routine determinations on a considerable number of patients would be justified.

Findings on the first 600 patients tested were published in 1935. My complete Milwaukee series included 763 women and girls and the results are shown in Table I.

TABLE I

Plus 35-40%	1	73 women or 9.6% above plus 10%
Plus 30-35	2	
Plus 25-30	8	
Plus 20-25	10	
Plus 15-20	19	
Plus 10-15	33	
Plus 5-10	56	339 women or 44.4% in normal range
Plus 1-5	69	
0	19	
Minus 1-5	80	
Minus 5-10	115	
Minus 10-15	121	351 women or 46% below minus 10%
Minus 15-20	116	
Minus 20-25	74	
Minus 25-30	32	
Minus 30-35	7	
Minus 35-40	1	

The Milwaukee series furnished basal metabolic rate evidence that a high percentage of the women and girls in that area had varying degrees of hypothyroidism. This series was closed when, in the Autumn of 1936, I moved into a locality where it was believed that most people had normal thyroids. However, in my new location, clinical evidence of abnormal thyroids caused me to begin taking an occasional basal metabolic rate, and after finding a few cases of mild myxedema and several patients with marked hypothyroidism of lesser degree, who had lived in Delaware from birth, I started a new series as a means of determining whether or not there might be a thyroid problem in the Delaware area. Table II records the findings in the first 263 women studied.

A comparison of the Wilmington and the Milwaukee series indicates that so far as can be learned from basal metabolic rate determinations there is as much of a thyroid problem in Delaware as in Milwaukee. Clinical tests with desiccated thyroid in both Milwaukee and Wilmington have indicated that for the most part women with a basal metabolic rate below minus 8 per cent are benefited by the use of small carefully regulated doses of thyroid.

Each series of tests included 126 pregnant women. A comparison of the two groups is possible, from the following:

MILWAUKEE
16.7% above plus 10%
52.4% in normal range
30.9% below minus 10%

WILMINGTON
5.5% above plus 10%
50.0% in normal range
44.5% below minus 10%

TABLE II

Plus 45-55%	1	} 20 women or 7.6% above plus 10%
Plus 40-45	1	
Plus 30-35	1	
Plus 15-20	5	
Plus 10-15	12	
Plus 5-10	15	} 120 women or 45.6% in normal range
Plus 1-5	19	
0	10	
Minus 1-5	29	
Minus 5-10	47	
Minus 10-15	55	} 123 women or 46.8% below minus 10%
Minus 15-20	38	
Minus 20-25	24	
Minus 25-30	5	
Minus 30-35	1	

The tables just presented suggest that hyperthyroidism may be more common in Milwaukee and hypothyroidism in Wilmington. However, my Wilmington group included a number of women with a low basal metabolic rate who consulted me because of abortions or sterility. There is also evidence that hypothyroidism is increasing in America, and it is possible that a series of tests made on pregnant women in Milwaukee today would show a higher percentage of low readings than were noted in my series made prior to 1936.

The basal metabolic rate determinations made for my 1926 paper on women late in pregnancy and just before they left the hospital following delivery, indicated that if a woman had a normal thyroid and took iodine during pregnancy, her rate would remain within normal limits. Since this observation did not agree with the reports of certain other observers a new study has been made in Wilmington on a fairly consecutive group of women who had the first test early in pregnancy, the second late in pregnancy and the third five or more weeks after delivery. A consecutive series was not possible as some women delivered prematurely while others for some reason failed to take the test late in pregnancy. The results of this study are shown in Table III.

TABLE III

Plus	10-15%	EARLY PREGNANCY		LATE PREGNANCY		POST PARTUM	
		1	2%	3	6%	0	
Plus	5-10	2		6		4	
Plus	1-5	3		8		2	
	0	2	56%	0	62%	0	48%
Minus	1-5	5		4		6	
Minus	5-10	16		13		14	
Minus	10-15	10		6		10	
Minus	15-20	6		6		8	
Minus	20-25	6	42%	4	32%	3	52%
Minus	25-30	0		0		3	

This table indicates that a slight increase in the basal metabolic rate may occur during pregnancy but, as in my 1926 report, the present study shows that women who have ample iodine during pregnancy

maintain a fairly stable rate far below that reported by Baer¹ in 1921 and Cornell² in 1923. The slight increase in the Wilmington series probably resulted from the administration of thyroid to all women who had a rate below minus 10 per cent and a few of the women in the minus 5 to 10 per cent group who also had thyroid in small doses.

An obstetric tragedy occurred in my practice during the present study. A patient whom I had delivered in Milwaukee three times became pregnant after a lapse of sixteen years and reported to my Wilmington office. Her first basal metabolic rate on June 25, 1941, was plus 18 per cent. Shortly before the onset of labor the rate was plus 32 per cent and her general condition was unsatisfactory. At the time I did not appreciate that she had a definite hyperthyroidism, but twelve hours after delivery she died with a type of cardiac failure observed with toxic goiter. It is possible that large doses of iodine during her labor might have influenced the outcome.

Three other patients with hyperthyroidism have been observed in my Wilmington office. Mrs. J. became toxic following an abortion, and Mrs. W. during the puerperium. Both women responded well to bed rest combined with the administration of iodine and phenobarbital. Mrs. B. whose first test was plus 55 per cent had a history of a thyroidectomy and roentgen-ray treatment of the thyroid. Her response to medical treatment was unsatisfactory and she was referred back to the surgeon who had performed the thyroidectomy.

Myxedema usually can be recognized from a thick dry skin, slow pulse, and subnormal temperature. Overweight is the rule, but Plummer,⁶ in 1940, reported that he had found in the examination of 200 cases of spontaneous myxedema 77, or 38.5 per cent, who were below the theoretical normal weight for their height. It has been observed that practically all patients who have a slow pulse and subnormal temperature have a low basal metabolic rate. Barnes,⁷ in 1942, reported that in over 1,000 cases in which the basal metabolic rate was subnormal, the body temperature was always subnormal unless an infection was present. This statement in general agrees with my own observations.

Interpretation of the basal metabolic rate may be difficult except in cases where it confirms clinical observations or furnishes a clue to the thyroid as a factor in the development of certain symptoms. A moderate increase of the rate above normal is not definite proof of hyperthyroidism. A decreased rate cannot result from emotional disturbances and it offers more reliable evidence of hypothyroidism, but it must be remembered that this may be a temporary condition secondary to an infection or other cause and that thyroid function may return to normal when the cause of the dysfunction is removed.

My observations during the past twenty years suggest that the thyroid problem in America may be changing, since a considerable portion of the population has received more iodine through the use of iodized salt preparations containing iodine, and in sea food. Only three of the first 35 women tested for me had low basal metabolic rates.

Ten years later 30.9 per cent of the pregnant women seen in my Milwaukee office had low rates, and in my Wilmington series 44.5 per cent were below normal. With the wide use of iodine in the so-called goiter areas, the incidence of thyroid hypertrophy and toxic goiter has materially diminished. In his discussion of Plummer's paper in 1940, Jackson said: "Our group, in Wisconsin, has seen more cases of hypothyroidism in the last five years than in the previous fifteen." It seems reasonable to postulate that a generation of women with abnormal thyroids has passed into a state of hypothyroidism without having the hypertrophy of the thyroid and toxic goiter so frequent a generation ago. While a new generation must grow to maturity before we can determine the effect of iodine therapy on the development of the thyroid during intrauterine life, we do know that it has practically eliminated hypertrophy of the thyroid at birth. Since prescribing iodine for every woman under prenatal care in my office, over 1,500 babies have been delivered with only one that had evidence of an enlarged thyroid at birth. Its mother was a sterility patient who had both iodine and thyroid during pregnancy. The hypertrophy was temporary and disappeared in a few weeks.

Cretinism is no longer a medical curiosity in America. In 1893, Osler was able to collect only 11 cases in the United States, but in 1934, Jackson was able to list 512 cases. New cases are being found each year and some fear that the present high incidence of hypothyroidism may lead to a rapid increase in the number of cretins. This may occur unless we promptly attack the problem through prenatal medication with ample doses of iodine.

DeQuervain is convinced that the harmful changes which may result from improper development of the thyroid are evident by the seventh month of pregnancy, hence the administration of iodine, and, when indicated, thyroid, to the pregnant woman should be started as early in pregnancy as possible. Preferably, the hypothyroid group of women should have treatment for some months before a pregnancy is attempted. For this group, iodine and thyroid medication has been proved to help overcome sterility and to lessen the risk of abortion. There is clinical evidence for believing that when iodine is available for the infant in utero its thyroid may contribute to the thyroxine needs of the mother during the last weeks of pregnancy.

Hypothyroid women have a number of annoying symptoms of which the most common are fatigue, weakness, nervousness, dry skin, falling hair, a tendency to constipation, overweight, menstrual disturbances, sterility, miscarriage, generalized pains, and joint pains. As previously stated, women with dry skin, subnormal temperature and slow pulse are clinically hypothyroid, and the basal metabolic rate will be found low in most cases.

People with abnormal thyroids are found in every part of the United States, and it seems evident that iodine prophylaxis should become

routine in all prenatal care regardless of the place of birth of the patient or her present habitat. Iodine may be administered in different ways, but my preference is for the syrup of hydriodic acid, five drops per day in water being given for a month and then a slightly reduced dose for the rest of the pregnancy. Through adequate medication during the prenatal period, it is believed that it will be possible to prevent thyroid dysfunction from becoming a serious problem in America.

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Discussion

DR. S. LEON ISRAEL.—The magnitude of the thyroid's influence on the physiology of the female generative organs is suggested in the fact that during puberty, a time when it achieves its greatest increment of growth, the average weight of the thyroid gland in females is twice as much as in males. It is difficult, however, to correlate this fact with the varying basal metabolic rates of adolescent girls. There is, moreover, no unanimity of opinion concerning the influence of the menstrual cycle on the basal metabolic rate. The lack of uniformity may result from the fact that the basal metabolic rate is influenced by too many external factors. The usually accepted normal variation of the basal metabolic rate is such that any reading between minus 15 and plus 15 is regarded as being physiologic. Dr. Davis chose in his studies to employ minus 10 and plus 10 as the limits of normality. I wondered whether he had made this choice consciously, because he was observing ambulatory patients, in whom the actual metabolic rate is probably 5 per cent lower than that obtained in bed-rested patients.

It would have been most interesting had Dr. Davis been able to compare his patients' rates with changes in their serum cholesterol. Even though the latter is considered a more accurate gauge of hypothyroidism than is the basal metabolic rate, it is difficult to perform repeatedly in office research. It is better to consider the patient with the lowered basal rate as hypothyroid, more especially if she then responds favorably to properly controlled and adequately administered doses of a known potent thyroid preparation.

Dr. Davis makes an important point when he reminds us that the interpretation of the basal metabolic rate may be difficult except where it confirms clinical observation. This is especially true in the treatment of menstrual disorders and sterility, wherein determination of the basal metabolic rate and, as confirmatory evidence, of the level of the blood cholesterol is essential. The typical signs and symptoms of hypothyroidism in terms of classical myxedema are rarely encountered. While it is true that a basal metabolic rate of minus 8 or minus 10 in normal women may be ignored, it is also imperative, as Dr. Davis states, to acknowledge that in ambulatory women with either a nonorganic menstrual dysfunction or sterility such slight diminution of the metabolic rate may be of telling value. Therapeutic trial with desiccated thyroid substance is always indicated in such patients. For the same reason, it appears logical to administer the substance to pregnant women having an initially low metabolism.

It is difficult for me to comment on Dr. Davis' thesis of a changing metabolic rate in American women as evidenced by consistently lower rates and a decreasing incidence of thyroid hypertrophy. His own statistics, those of this presentation as well as his widely-quoted earlier ones, attest the usefulness of iodine in maintaining normal metabolic levels in pregnant women. An incidence of only 6 per cent of patients with increased rates late in pregnancy is strikingly low in comparison with most other series, an effect which Dr. Davis attributes to the exhibition of iodine. May I ask, in closing, that Dr. Davis clarify the reason for wishing to control the elevation of the basal metabolic rate of late pregnancy, an increase which seems to stem from the physiologically increased mass of mother and fetus.

DR. DAVIS (closing).—Cholesterol determinations were not made owing to the expense involved. As suggested in my paper, it is my belief that some of the earlier conclusions regarding the increase in the basal metabolic rate during pregnancy are not correct. I made inquiries regarding the Mayo Clinic report and found that the patients did not take any iodine during pregnancy. It is my contention that if a patient with a normal thyroid has adequate iodine during pregnancy her basal metabolic rate will remain within normal limits. The administration of iodine is of major importance for the infant in utero.

I have not been able to confirm the conclusions reached by Dr. Bartholemew in regard to the relation of the thyroid to toxemia.

I summarized the last hundred records of women tested since this paper was written last summer and found that 6 had a basal metabolic rate above plus 10 per cent, 46 were within the normal limits and 48 were below minus 10 per cent. My single plea is for the routine administration of iodine to all pregnant women.

AN ATTEMPT TO CORRELATE THE PRE-ECLAMPTIC STATE WITH A CONGENITAL ANOMALY OF THE KIDNEY*

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MUCH as we pride ourselves on the decrease in the mortality rate in eclampsia, since Stroganoff, the fact remains that there has not been a reduction in the number of cases of pre-eclampsia. The pre-eclamptic state is still with us in spite of the extensive drive in social education resulting in more adequate prenatal care.

One is impressed, first, by the advent of the pre-eclamptic state with the first pregnancy, regardless of age; second, by the frequency with which it recurs in succeeding pregnancies; third, by its characteristic appearance in the last trimester; fourth, by the great number of patients who early have few subjective symptoms, the only objective symptom being hypertension, with few if any urinary findings, and last, by the rapidity with which the blood pressure so often returns to normal six or eight weeks after the termination of the pregnancy. Why?

*Presented at a meeting of the Philadelphia Obstetrical Society, November 5, 1942.

A possible clue was offered by Goldblatt's work¹ on renal ischemia. The similarity between the findings in the experimental animals after moderate clamping of the renal artery and in the early pre-eclamptic state is striking. There was little or no change in the general condition of the experimental animal except for hypertension, little or no impairment in the excretory function of the kidney, no change in blood chemical findings and, finally, complete return to normal with removal of the clamp on the renal artery.

A more recent clue was offered by Campbell² and others who observed that men with prostatic hypertrophy and intrarenal kidney pelves had marked hypertension, in comparison with similar patients who had extrarenal kidney pelves. When decompression was slowly carried out in those cases with intrarenal pelves, the blood pressure level returned to normal, and after prostatectomy it remained normal.

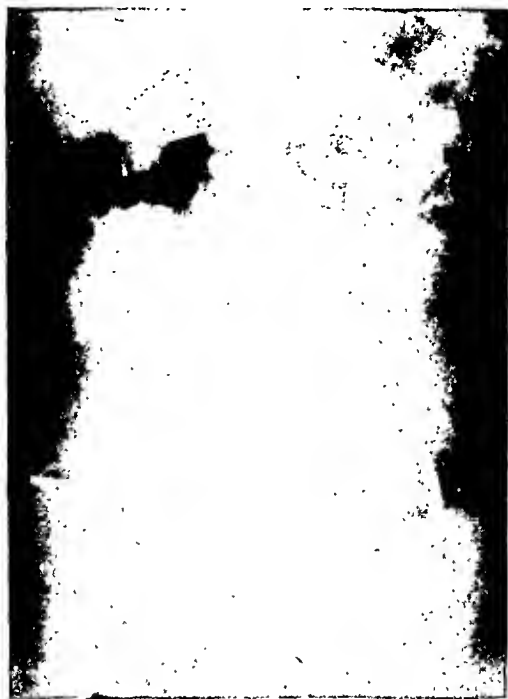


Fig. 1.—Kidney with a typical extrarenal pelvis.

With these clues in mind we attempted to correlate the accepted "arteriolar spasm theory of pre-eclampsia" and the anatomic location of the renal pelvis.

We are all aware of the marked dilatation which occurs in the ureter and renal pelvis during pregnancy, even as early as the tenth week. Whether this is secondary to hormonal action or caused by pressure of the enlarging uterus upon the pelvic ureter is not of importance in this discussion. The facts that there is dilatation of the entire ureter and that the maximum dilatation occurs in the renal pelvis are important in that this dilatation may compress the kidney medulla and thus increase the intrarenal pressure, with resulting tissue ischemia.

We are aware that the capacity of the ureters and renal pelvis in the nonpregnant state is 15 c.c., while at term the capacity varies from 32 to 84 c.c. The capacity of the renal pelvis is greater than the combined capacities of the calices; that is, the larger the renal pelvis the smaller the calices, and vice versa.

A kidney pelvis is defined as intrarenal if more than 50 per cent of the pelvis is inside a line drawn from the lateral aspect of one pole of the kidney to the lateral aspect of the other pole on the side of the ureteral attachment.

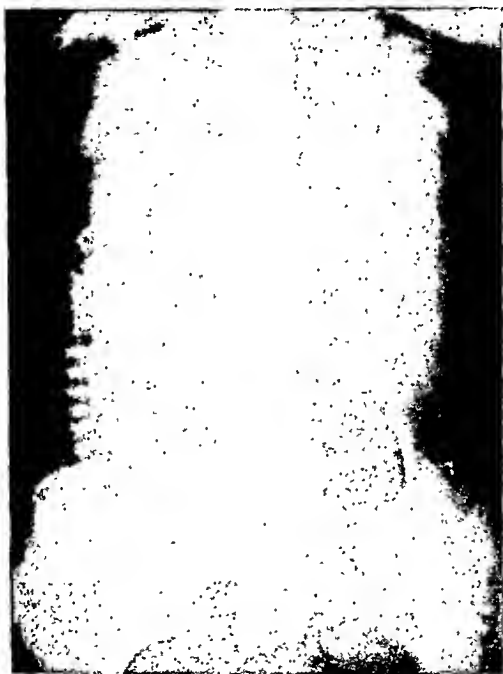


Fig. 2.—Kidney with a typical intrarenal pelvis.

Material and Methods

The material for this report consists of 74 cases, divided into three groups.

1. Twenty-two consecutive patients with pre-eclampsia over a period of six months admitted to the obstetric department of Hahnemann Hospital. The criterion of toxemia was persistence of systolic blood pressure of 140 mm. or more after a forty-eight-hour rest in bed. No case was included in which the blood pressure level was elevated before the fourth month of pregnancy.

2. Twenty-five cases of uropathic conditions complicating pregnancy, on the same service during the same period of time. All cases were nontoxic.

3. A selected group of controls consisting of 27 normal pregnant women near term, who delivered without showing any toxic phenomena.

Routine intravenous urograms were made in all 74 cases. With one exception, all patients were followed to term or termination of pregnancy. The roentgenograms were read by a member of the x-ray department who was intentionally deprived of any knowledge of the clinical status of the patients. He was asked to state whether the kidney pelvis were intrarenal or extrarenal. After all roentgenograms were read, the clinical status was correlated with the roentgenologic status. The following results were obtained: Of the 22 toxie cases, 20 patients had intrarenal pelvis and 2, extrarenal pelvis.

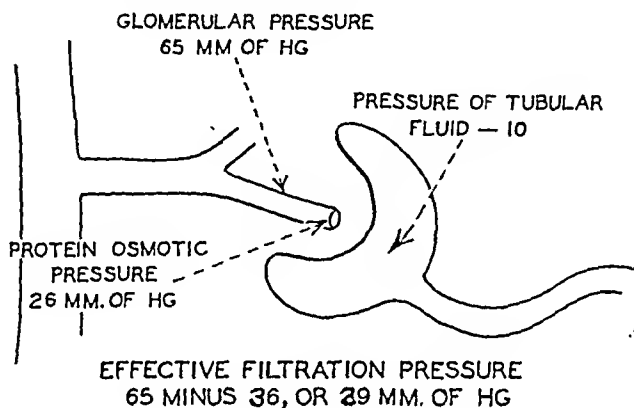


Fig. 3.—Normal glomerular physiology.

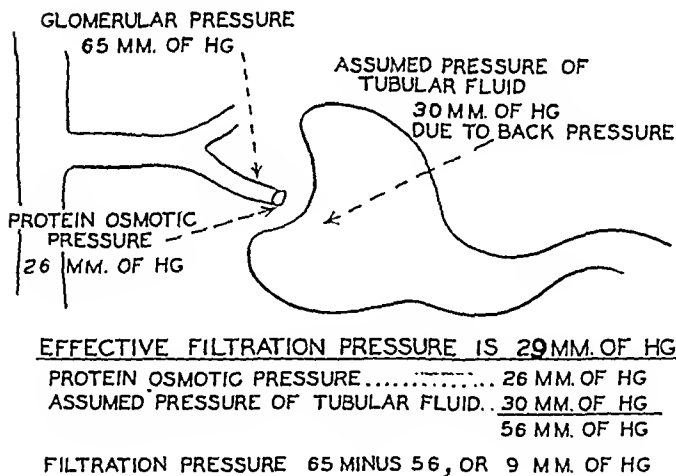


Fig. 4.—Abnormal glomerular physiology.

Of the two with extrarenal pelvis one was a patient with a fifth pregnancy at term with a mild toxemia, who in her four previous pregnancies had shown no evidence of the pre-eclamptic state. The other patient was a primipara in whom symptoms of pre-eclampsia developed in the thirty-eighth week. The blood pressure rose to 165 mm. systolic and 80 mm. diastolic, where it persisted for three days and then subsided, and she was delivered at the fortieth week, with a normal blood pressure. Urinary findings were negative.

Of the 25 patients with uropathic conditions complicating pregnancy who did not have toxemia at the time the urograms were taken, 17 had extrarenal pelves, and 8, intrarenal pelves.

All of the 17 patients with extrarenal pelves delivered without showing any elevation in blood pressure or other symptoms of the pre-eclamptic state.

Of the 8 patients who had intrarenal pelves, with normal blood pressure readings, etc., at the time the urograms were taken, one case was lost in the follow-up and in another, a primipara, intra-partum eclampsia developed.

Of the 22 toxic cases, there were 14 primiparas and 8 multiparas. The multiparas were divided as follows:

NUMBER OF PREGNANCIES	CASES
2	1
3	4
4	1
5	2

Of the 8 multiparas in the group with toxemia, there was a history of previous pre-eclampsia in 5. Of the 8 cases, 7 patients had intrarenal pelves and one had an extrarenal pelvis. The one case with extrarenal pelvis was in her fifth pregnancy at term; the patient had no previous history of pre-eclampsia.

In the normal control group, totaling 27 cases, there were 18 with extrarenal pelves and 9 with intrarenal pelves.

Discussion

Can these findings be correlated with our present knowledge of renal physiology?

Goldblatt had produced hypertension by partially clamping the renal arteries in his experimental animals. It makes little difference whether the hypertension was caused by a compensatory rise in blood pressure because of the necessary increase in the rate of blood flow to the ischemic kidney or whether it was the result of a nervous reflex in the ischemic kidney or brought about by the production or storing up of a substance which Goldblatt suggests might be called renin, which acts somehow to cause arteriolar spasm. The fact remains that a decreased flow of blood results in hypertension (Fig. 3).

1. The normal glomerular pressure is 65 mm. of mercury.
2. In the normal kidney the pressure of the tubular fluid is 10 mm. of mercury.
3. All the plasma with the exception of proteins can pass through the permeable membrane of the glomeruli by filtration.
4. A pressure above 26 mm. of mercury is necessary for filtration of the protein elements of the plasma, the so-called colloidal or protein osmotic pressure.
5. Therefore, the filtration pressure may be considered the glomerular pressure minus the total of the colloidal or protein osmotic pressure and the pressure of the tubular fluid; in other words, 65 minus 26, plus 10, or 29, is the effective filtration pressure.

Since normally the kidney pelvis is dilated in pregnancy, we assume that in the presence of an intrarenal kidney pelvis the resulting increased intrarenal pressure must of necessity cause back pressure in the kidney tubule, which in turn must be compensated for by an increase in glomerular pressure or, in other words, an increase in blood pressure.

If the above hypothesis be true, let us assume that something like this occurs (Fig. 4).

Instead of a normal pressure of tubular fluid of 10 mm. of mercury let us assume that the pressure is 30 mm. of mercury, due to back pressure from a distended intrarenal pelvis. The colloidal, or protein, osmotic pressure of 26 mm. of mercury is added to the pressure of tubular fluid of 30 mm. of mercury, the result being 56 mm. of mercury. The filtration pressure is now calculated and found to be 65 minus 56, or 9 mm. of mercury. As previously stated, 29 mm. of mercury is the effective filtration pressure.

Therefore, we theorize that of necessity the vicious circle is broken in only one way, and that is by raising the glomerular pressure, or in other words, the blood pressure.

Conclusion

In a small series of cases, it has been shown that an intrarenal pelvis is more common in the pre-eclamptic state than in normal pregnancy, or even in patients with uropathic conditions complicating pregnancy. An hypothesis is offered to explain these observations. The series is too small to arrive at any definite conclusion. It is necessary to accumulate further data.

Acknowledgments are made to Dr. Edward W. Campbell, for his original suggestion, to Dr. John Scott for his aid in applying the physiology of the kidney to our observation, to Dr. Harry Evans, Sr., of the Department of Roentgenology, and to Dr. Newlin F. Paxson for his advice.

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250 SOUTH 18TH STREET

Discussion

DR. NEWLIN PAXSON.—Dr. Hunter's observations in a small series of cases show that the average ratio of extra- to intrarenal pelvis is approximately 2 to 1 in normal pregnancy, while in toxemic cases the ratio is about 9 to 1 in favor of intrarenal pelvises. These observations might be coincidental, but such observations stimulate the imagination. One must ask whether there is an actual back pressure in the ureters? Dr. Hundley, of Baltimore, has shown that in pregnancy there is hypertrophy of the ureters but he did not measure the pressure, but simply created an artificial back pressure to put tension on the ureters to measure rhythmical contractions.

One method of studying this problem would be to take urograms in young married women to see if a prediction of toxemia could be made. All that would be needed would be one intravenous urogram.

FAVORABLE RESPONSE OF ADVANCED ENDOMETRIOSIS TO TESTOSTERONE PROPIONATE THERAPY*

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THIS report consists of the following: (1) Summary of information from the literature establishing a rational basis for the use of androgens for endometriosis; (2) description of a unique personal case in support of a hyperplasia causative factor of endometriosis; (3) results of hormone therapy in two cases of advanced inoperable disease.

Experimentally, marked progesterone-like effects of androgens have been demonstrated in female rats and rabbits; and ovarian and endometrial atrophy with suppression of menstruation has been produced in monkeys.¹ Rothermich and Foltz² showed that androgens reduced urinary gonadotropic hormones in menopausal women.

Following W. O. Wilson's production by prolonged estrogen administration in guinea pigs of subserous fibromyomas resembling human fibroids, Lipschütz³ not only produced similar uterine and extragenital tumors, but also proved antifibromatogenic and antiestrogenic effects of both testosterone propionate and progesterone. Therefore, since hyperplasia endometrii often accompanies both uterine myomas and endometriosis in women,⁴ it would appear from the above that there is definite experimental basis for the use of androgens (and progesterone) in both conditions.

Clinically, there is little in literature concerning the use of androgens for endometriosis, and nothing about progesterone. Greenhill and Freed¹ successfully treated dysmenorrhea, functional uterine bleeding, premenstrual migraine and painful breasts with androgens, but did not include endometriosis. Reports on the use of androgens for fibromyomas give variable results, although except in the case of submucous myomas, excessive bleeding without much effect on the tumors has been reduced.⁵ However, we have produced definite involution of the uterus and small fibroids in recent cases.

Aub and others^{6, 7} believe that correction of abnormal estrogen overbalance by artificial increase of normally secreted androgen will provide hormone control of certain conditions in women.

Geist and Salmon⁸ secured favorable results in over four hundred cases of functional uterine bleeding and dysmenorrhea, premenstrual mastopathies, post-partum breast engorgement, and certain menopausal disturbances (without much masculinizing side effect) using less than 300 mg. of testosterone per month. Their results were attributed to suppression and/or nullification of ovarian estrogens, plus inhibition of endometrial proliferation, of reactivation of uterine musculature, and of hypophyseal gonadotropic activity. These authors also mention the rationale of androgen treatment of *early* endometriosis based on growth-stimulating effect of estrogen (and progesterone), but give no account of its use in actual disease.

*Read at a meeting of the Philadelphia Obstetrical Society, December 3, 1942.

In all reports, effectiveness of synthetic testosterone compounds appeared to be equal whether given intramuscularly as the propionate, orally as methyl tablets, sublingually in propylene glycol, subcutaneously or subfascially in pellets. The last method holds little advantage and some risk of tetanus implantation (Weleh⁹). Results were checked not by output control such as the chick-comb method (Frank and others¹⁰), or the colorimetric titer (Hamblen and others¹¹), but therapy was gauged by clinical response, plus endometrial and/or vaginal biopsy.

There is but one reported case of treatment of endometriosis by androsterone.¹² Wilson describes a para i, aged 28 years, pain in rectum and thigh for eight months due to endometrial cystoma of the rectovaginal septum proved by biopsy. Through 4,500 mg. of testosterone propionate injected throughout twelve months, this woman's normal menstrual flow was reduced to staining for one to four days every other month, pain was completely relieved, the endometrioma reduced to one-third original



Fig. 1.—Uterus from girl of 19 years, with solid lower uterine segment and cervix, rudimentary blind vagina, secretory endometrium, and fresh corpus luteum at operation. There was no trace of endometriosis in this patient.

size, uterine mucosa atrophied, but cervix, breasts, and vaginal biopsy, as well as libido, were unchanged. However, the voice became husky, habitual hirsutism, and clitoris greatly increased, but secretory endometrium was found five weeks after treatment ceased, and normal menstruation appeared one week later, continuing for six months. Unfortunately, both the pain and endometrial cystoma resumed original proportions.

Certain additional facts suggest a hyperplasia factor in the development of the generally accepted misplaced endometrial cell mechanism (Sampson) of endometriosis. Undoubtedly in addition to myoma uteri,¹³

posterior uterine displacement,²¹ surgical implantation,¹⁴ extensive pelvic examinations and tubal insufflations near menstrual times,¹⁵ cervical stenosis, etc., are activating factors. But delayed and infrequent child bearing,^{16, 17} as well as proved endometrial hyperplasia in both menstrual and menopausal¹⁸ ages are probable predisposing causes. It is significant that in our large gynecologic ward service of the Philadelphia General Hospital, despite high incidence of myomas, there is relatively little endometriosis, probably due to frequently associated pelvic inflammatory disease. We believe that the high sterility incidence (40 per cent.)¹⁹ of endometriosis is a primary dysfunction and not secondary.

In support of hyperplasia as a predisposing cause is one of our private patients, aged 19 years, who presumably for three years had been menstruating painfully into the peritoneal cavity. At operation, there were widely patent tubes, normal ovaries (one with fresh corpus luteum), uterine fundus and endometrium, but a completely solid lower uterine segment and cervix connecting with a rudimentary blind vagina via a thin cord. There was no trace of endometriosis, and this young woman was completely relieved by total hysterectomy with conservation of the ovaries.

Treatment of endometriosis is difficult, since preservation of child-bearing and menstrual functions often conflict with radical excisions or irradiation castration, often essential for cure. Although in young women, partial excisions, uterine suspension, cervical dilatation and cauterization, may be helpful, heretofore subsequent radical procedure has been inevitable, especially since presacral sympathectomy is contraindicated (Hurd²⁰). Therefore, the treatment and results of two inoperable cases of advanced pelvic endometriosis given below are offered as further evidence of a hyperplasia factor as well as temporary solution of a difficult situation.

Case Reports

CASE 1.—Patient, aged 33 years, married 7 years, birth control 4 years, no conception. Menses 12, 26/4, no pain; basal metabolic rate -19 to -7. Only complaint, sterility. *Diagnosis:* Adherent acutely retroflexed uterus.

Feb. 14, 1939: Operation: Dilatation and curettage, hyperplasia; right chocolate cystectomy (bilateral endometriosis, adherent); right salpingectomy; appendectomy; Coffey uterine suspension. Pathologic report: Tubal endometriosis.

Aug. 6, 1940: Delivered of normal male infant, 7 pounds 13 ounces, by manual rotation, low forceps extraction; good recovery. Sept. 23, 1940: Good postnatal condition.

Oct. 1, 1940, Jan. 22, 1941, and March 7, 1941: Nothing significant. Sept. 3, 1941: Enlarged left ovary.

Feb. 11, 1942: Menstrual history: 21/14/3, scant; basal metabolic rate, ± 2 per cent. Small "solid" left ovarian cyst.

March 30, 1942: Rubin test. O.K. Menses: 27-23/short.

June 30, 1942: Left ovarian endometrial cyst *larger*, operation refused. Oreton* 125 mg. per month, intramuscularly, begun.

Sept. 18, 1942: Menses 24/21/4 scant, ovarian cyst behind uterus *larger*, oreton increased (25 mg., q. third day).

Oct. 27, 1942: Menses 24/31½; uterus and left cystic ovary definitely smaller. Treatment continuing as above.

CASE 2.†—*First Admission*: August, 1934, unmarried, aged 23 years; menses, normal; persistent leucorrhea, general abdominal pain, some abdominal rigidity, chief tenderness in right lower quadrant; temperature, 100° F.; white blood count, 13,000.

Operation: Abdomen full of chocolate fluid from ruptured whitish right ovarian cyst, removed with tube and appendix, clinically endometrial, pathologically same (?). Heetic recovery.

Second Admission: July 19, 1939, still single, well until intermittent abdominal pain two weeks, since onset of last period, leading to vomiting all food for last three days; red blood count, 5,500,000; white blood count, 11,500.

Diagnosis: Intestinal obstruction associated with large cyst in left pelvis.

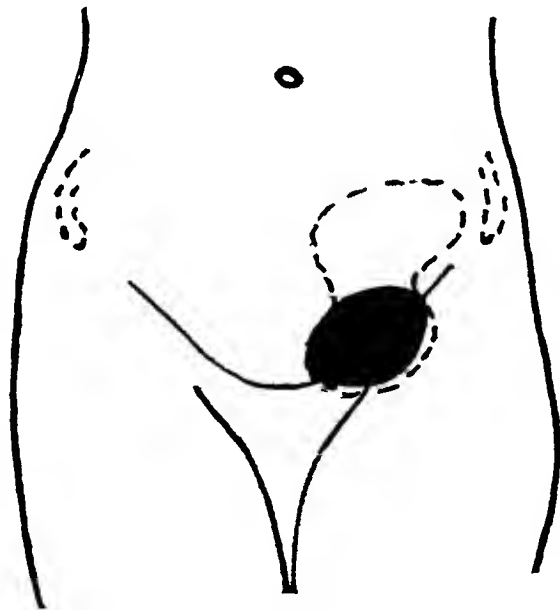


Fig. 2—Reduction of large ovarian endometrioma after treatment by testosterone propionate.

Operation: July 20, 1939, relief of obstruction of ileum adherent to large chocolate cyst of left ovary, which was opened and the pelvis drained (patient refused removal of ovary).

Subsequent History: Married July, 1941; painful menstruation and dysuria, 5 months; pain and obvious swelling in left lower quadrant, due to "dumbbell" shaped tender cystic mass in left pelvis, occupying lower abdomen to 3 fLÖ and associated with gaseous distention. Uterus larger than normal, fixed, good position. Weight 112 pounds. Hemoglobin 71 per cent.

*Supplied by the Schering Corporation.

†Through courtesy of Dr. Robert McElroy, from the service of Dr. L. Kraer Ferguson, Philadelphia General Hospital.

Intramuscular injections of Oreton* were given as follows:

May 26 to June 19, 1942, 80 mg. in 10 mg. doses. Felt much better by the fifth injection. Weight 108 $\frac{3}{4}$.

June 22 to July 10, 1942, 150 mg. in 25 mg. doses. Pain less severe; menses less, first day.

July 13 to Nov. 23, 1942, 2,050 mg. in 50 mg. doses; 100 mg. per week to Sept. 14, 1942, 150 mg. per week thereafter with the following effects:

July 13, 1942: Breasts smaller; voice husky, occasionally deep.

Aug. 3, 1942: Menstrual flow much less in amount. Left abdominal mass much smaller, so that "clothes fit for first time in a long while, and I feel flatter." Weight 110 $\frac{1}{4}$. Libido: same.

Aug. 17, 1942: Feels fine; clitoris (glans and prepuce) much enlarged, one month. Blood pressure 112/60; pulse 62, temperature 97.4° F. Cystic mass about two-fifths original size.

Aug. 30, 1942: Menses five days late, scant, some premenstrual pain.

Sept. 14, 1942: Still aware of small lump in left lower quadrant; voice hoarse.

Oct. 2, 1942: No pain. Menstruated Sept. 27, 1942, one day. Mass same as Aug. 17, 1942. Clitoris still larger. Uterus *small*.

Oct. 27, 1942: Habitual leucorrhea better; same left paraumbilical pulling pain noticeable as after first operation (due to regression of mass?). Some hirsutism, lip, leg, and abdomen (two weeks).

Nov. 23, 1942: No menses since Sept. 28, 1942, but cramps Nov. 21, 1942. Hirsutism increased. Voice deeper and huskier, chiefly with use; weight 113; breasts: distinctly smaller; clitoris still larger; libido less (little); mass same or slightly larger than at last examination (Oct. 2, 1942).

Comment.—Since this patient refused cystophorectomy or irradiation, androgen hormone therapy was the only available agent, and gave relief of pain and comfort which much more than compensated for secondary effects, so that not one injection was missed in nearly six months of treatment.

We are continuing treatment in tablet form in decreasing dosage to establish minimal requirement by subjective symptoms and objective signs, rather than excretion values; and due to similar antiestrogenic and antifibromatogenic action of both testosterone propionate and progesterone, as well as to known associated endometrial hyperplasia, we plan to substitute progesterone for testosterone, to be reported later.

Conclusions

1. Intramuscular injections of testosterone propionate have a rational basis for the conservative treatment of endometriosis.

2. Large amounts are necessary for the relief of pain and reduction of swelling.

3. Complete absorption of large endometrial masses is not possible in a few months' treatment.

4. This type of treatment is practical for advanced cases where radical excision is contraindicated or refused.

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500 NORTH TWENTIETH STREET

COMBINED X-RAY AND EXTERNAL PELVIMETRY*

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WHEN we adopted x-ray pelvimetry at the Boston City Hospital four years ago, we set out to get the most possible information in the simplest manner. We planned to omit all kinds of elaborate apparatus and highly technical details and develop a system of pelvimetry which could be used by any practitioner with the aid of simple x-ray films.

The simplest technique seemed to be the mathematical calculation method originally devised by Ball¹ and modified by Snow.² In this method simple anteroposterior and lateral films are taken. The diameters and correction factors are measured directly on the films and the mathematics involved done by the Ball calculator or the slide rule devised by Snow and Lewis.

Material

We used this technique in 200 unselected primiparas, satisfactorily checking our measurements by the Thoms³ method and by direct measurements at operation, and the findings were reported in 1940.⁴ Since then we have used x-ray pelvimetry in selected cases only, latterly changing our technique somewhat by using it in conjunction with external pelvimetry which we have developed in more detail, especially with regard to the subpubic arch and outlet. We feel, following the dictum of DeLee, that x-ray pelvimetry should supplement and not supplant external pelvimetry and clinical examination of the pelvis.

*Read at a meeting of the New England Gynecological and Obstetrical Society at Boston, December 2, 1942.

The pelvic canal, for all practical purposes, may be divided into 3 planes, the inlet, midpelvis, and outlet, and bony dystocia may be encountered at any one or all of these levels. The study of the bony pelvis involves consideration of contours and measurements. Normal measurements with abnormal contours may cause dystocia just as normal contours with small measurements. Although there is yet no perfect means of measuring the fetal head in utero, we know the variations in its size may vary but slightly despite considerable variations in fetal body weights. If a head departs markedly from the normal this can be diagnosed as a rule by abdominal palpation and the head may be measured

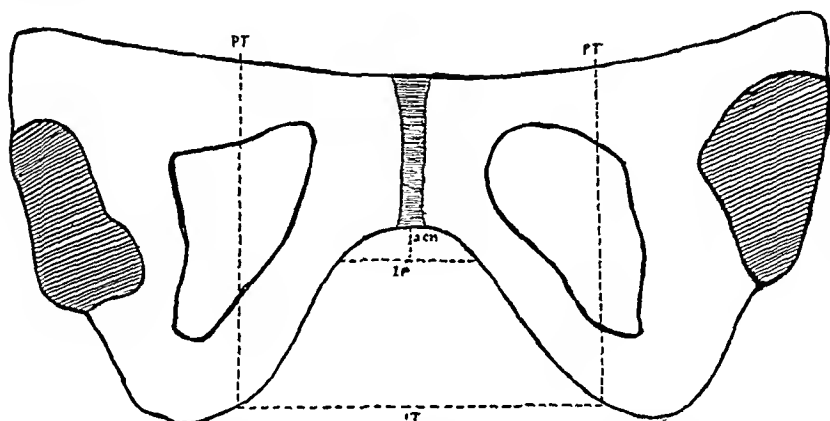


Fig. 1.—Diameters of pelvic outlet: *IP*, interpubic; *IT*, intertuberos; *PT*, pubo-tuberos.

fairly satisfactorily through the abdominal wall. If the head is engaged or if it is fixed well in the lower uterine segment even before engagement, it may be measured quite accurately by the Ball technique.

Our present method of investigation for cephalopelvic disproportion, preferably done within two weeks of the expected date of confinement, or better at the onset of labor, consists of (1) external pelvimetry, (2) estimation of fetal head size, and (3) x-ray pelvimetry if indicated.

External Pelvimetry

The intereristal, interspinous, external conjugate, and intertrochanteric diameters are measured. If the external conjugate is less than 18.5 cm., we suspect possible narrowing of the conjugate vera. The subpubic arch and outlet are palpated carefully and the following diameters are measured, using the DeLee or Pieri outlet pelvimeters. (The Thoms' outlet pelvimeter cannot be used for the subpubic arch.)

The interpubic diameter is taken on the subpubic arch 2 cm. (about a thumb's breadth) below the lower border of the symphysis and $\frac{1}{2}$ cm. is added to allow for soft tissue thickness (Fig. 1). It is at this plane that the occipital diameter of the fetal head impinges in the process of extension (Fig. 2). Since the occipital diameter of the fetal head usually measures 6 cm., an interpubic diameter less than 6 cm. would require impingement of the occiput lower in the arch with possible dystocia. Since the pubic origin of the levator ani muscles is located in the upper aspect of the arch, a narrow arch would also indicate a narrowing of the fore part of the sling formed by the levators for rotation of the head at midpelvis which might cause dystocia at this level.

The intertuberos diameter is taken between the most medial points of the tuberositis of the ischium and 1 to 2 cm. added for soft tissue thickness. It is at this plane that the biparietal diameter of the fetal head normally emerges, but if it or the arch is small the biparietal diameter may be forced well below it, causing considerable stretching of the perineum with possible severe lacerations unless anticipated by a generous episiotomy. If the intertuberos diameter is less than 9 cm. we measure the posterior sagittal diameter of the outlet, the sum of the intertuberos and posterior sagittal being necessarily 15 cm. or dystocia is suggested and cesarean section probably indicated.

The pubotuberos diameter of Schumann⁵ is taken perpendicularly upward from the most medial point of the tuberosity of the ischium to the superior ramus of the pubis and is the measurement of the length of the forepelvis. If this measurement is over 11 cm. we consider the pelvis abnormally long and investigate for a possible funnel-pelvis.

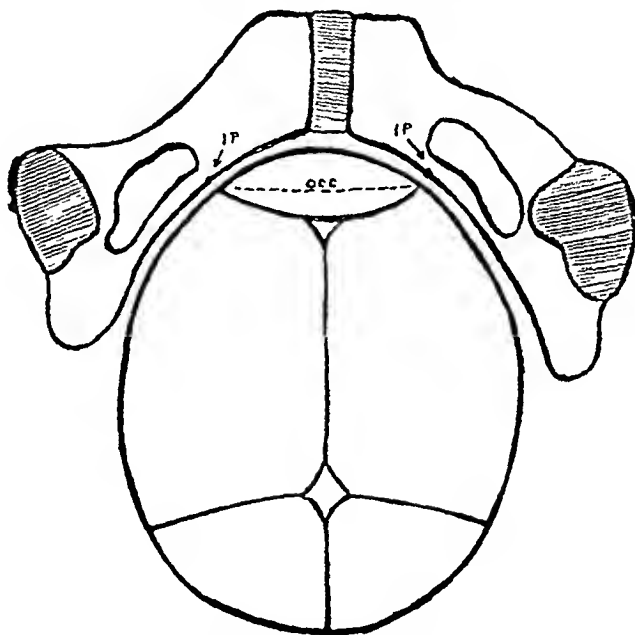


Fig. 2.—Relation of occiput to interpubic diameter: *Occ*, occipital diameter; *IP*, interpubic diameter.

OUTLET (300 CASES)

Intertuberos:	6 cm. or over	88%
	Under 6 cm.	12%
Intertuberos:	Over 9 cm.	84%
	9 cm. or under	15%
	Under 8 cm.	1%
Pubotuberos:	11 cm. or under	80%
	Over 11 cm.	20%

The posterior sagittal is taken only if the intertuberos is less than 9 cm. and is measured from the midpoint of the intertuberos diameter to the back of the sacrococcygeal junction, 1 cm. being subtracted to allow for the thickness of the bone.

The patient then lies on her side and the width of the sacrum estimated and the sacrococcygeal junction palpated for any abnormalities. Re-

cently we have added to our study the posterior transverse diameter of the inlet as suggested by Steele and Javert.⁶ This is taken from the most medial aspect of the dimples on either side of the rhomboid of Michaelis and helps in differentiating between the gynecoid and android pelvises.

Estimation of Fetal Head Size

The usual palpation for determination of engagement of the head is performed. The occipitofrontal diameter of the head is measured directly through the abdominal wall if feasible. Estimation of conformity of the fetal head to the pelvic inlet may be ascertained by using Kerr's technique by which the left index finger in the patient's rectum determines the descent of the head effected by pressure from above the symphysis.

FETAL HEADS (300 CASES)

Occipital:	6 cm. or under	98%
	6.5 cm.-7 cm.	2%
Biparietal:	9.5 cm. or under	94%
	10 cm.-10.5 cm.	6%
Occipitofrontal:	11 cm. or under	84%
	11.5 cm.-12.5 cm.	16%

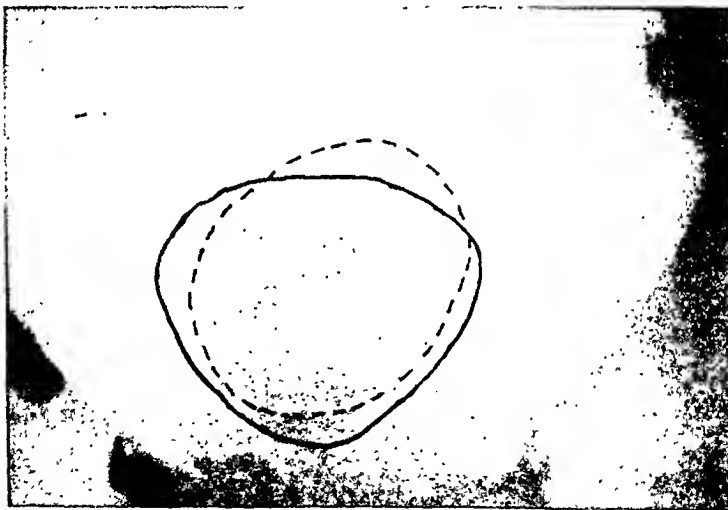


Fig. 3.—A.P. film of inlet with patient in semirecumbent position.

X-Ray Pelvimetry

The following criteria determine the need for x-rays:

1. Primiparas with floating heads at term.
2. Multiparas with a history of previous difficult deliveries.
3. Primiparous breeches with apparently small pelvis by external measurements.
4. Cases with narrow subpubic arches and outlets.
5. Elderly primiparas with external conjugates of 18.5 cm. or less.

Since the contour of the pelvic inlet is of paramount importance and since from our experience the most important diameter of the inlet is

the conjugate vera and that of the midpelvis is the posterior sagittal or width of the greater sciatic notch, we have directed our technique to a study of these factors. Thus, we take a film directly through the pelvic inlet with the patient semirecumbent to get a good view of the contour of the inlet (Fig. 3). The inlet is then classified according to the classification of Caldwell and Moloy.⁷ A true lateral film is then taken on which we measure the conjugate vera, the anterior sagittal, posterior sagittal, and anteroposterior diameters of the midpelvis, the pubotuberous diameter, and biparietal diameter of the fetal head if possible (Fig. 4). The correction factor for object-table top distance for all these latter measurements which are in the same sagittal plane is one-half the introchanteric diameter which we have already taken by external pelvimetry. To this measurement the table top-film distance is added to obtain the object-film distance. The mathematics is completed by the Ball calculator, by the Snow and Lewis slide rule, or by the simple mathematical formula, $O = I \frac{D - d}{D}$ in which O is the object; I the magnified image as measured on the film; D the target-film distance, and d the object-film distance.

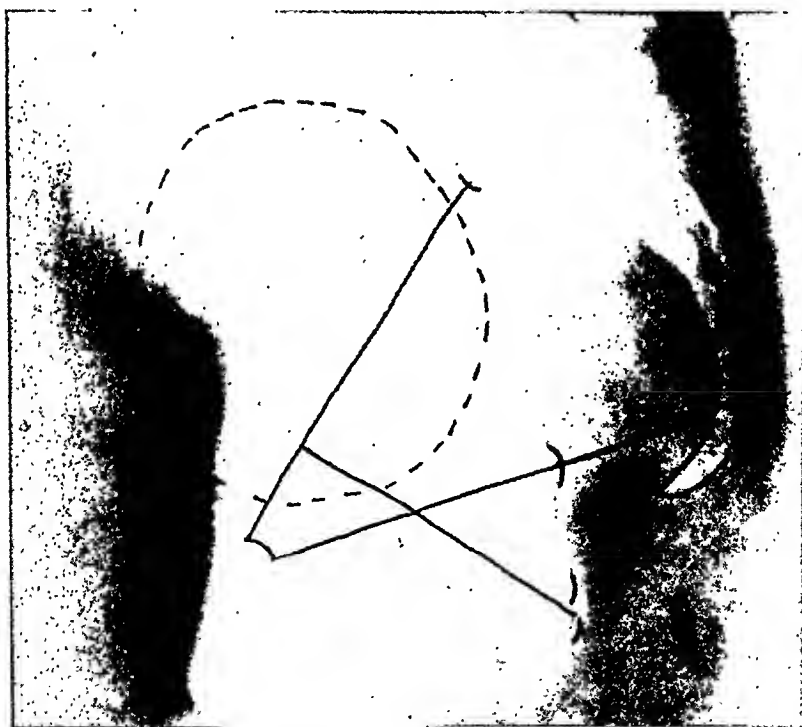


Fig. 4.—Lateral film with lines showing A.P. of inlet, anterior sagittal and posterior sagittal of midpelvis, and pubotuberous, of fore pelvis. Broken line indicates position of head.

Assuming the fetal head to be average in size, the question of probable dystocia at the various planes can be reduced to the following simple observations:

DYSTOCIA AT INLET—MEASUREMENTS

Conjugate vera under 10 cm. in generally contracted pelvis
 Conjugate vera under 9.5 cm. in flat pelvis

CONTOUR

Angulation of forepelvis
 Flattened posterior pelvis

Since the head enters the pelvic inlet in the majority of cases in an attitude of lateral flexion with the sagittal suture running transversely across the pelvis, the presenting fetal head diameter is the supraparietal-subparietal diameter which normally measures 8 cm. to $8\frac{1}{2}$ cm. thus allowing engagement of the head in even quite narrow anteroposterior diameters. If the forepelvis is acutely angulated, the head is crowded more into the posterior pelvis thus diminishing considerably the available anteroposterior diameter. The flattened posterior pelvis encroaches on the greatest transverse diameter of the inlet necessitating the long axis of the fetal head entering the inlet through a more anterior transverse diameter which may be markedly reduced in size due to the converging walls of the forepelvis.

DYSTOCIA AT MIDPELVIS—MEASUREMENTS

Posterior sagittal under 3.5 cm.
 Subpubic arch under 5.5 cm.

CONTOUR

Converging sacrum and pubis
 Sacrocoxygeal platform

If the head is engaged, we may assume that the patient will deliver from below but we must endeavor to anticipate trouble at the midpelvis and the outlet. If the subpubic arch is narrow we may suspect acuteness anteriorly in the midpelvis with delayed rotation which may also be caused by a narrow posterior sagittal diameter. In these cases x-rays would be indicated to measure the posterior sagittal diameter of the midpelvis and also to note any convergence of the sacrum and pubis and whether the sacrocoxygeal junction is angulated in a manner to interfere with descent of the head. If the head is engaged and the arch is normal or large, there is no need for x-rays since the adequate arch would compensate for a narrow interspinous or a narrow posterior sagittal diameter of the midpelvis.

DYSTOCIA AT OUTLET—MEASUREMENTS

Interpubic under 5.5 cm.
 Intertuberous under 9.0 cm.
 Pubotuberous over 11.0 cm.

CONTOUR

Acute rather than obtuse arch

A narrow arch will necessitate lower descent of the head to find an adequate diameter for impingement of the occiput in the process of extension. This might require a long episiotomy and traction well downward on the pelvic floor before horizontal traction is applied to bring the occiput under the arch. A narrow bituberous also will cause recession of the head necessitating a wide episiotomy. A pubotuberous diameter more than 11 cm. suggests a possible funnel pelvis. If the intertuberous and posterior sagittal diameters combined are less than 15 cm., the possibility of cesarean section must be considered.

Results

The advantages of our methods are best illustrated by the more conservative management of the so-called borderline cases and the decrease in the number of cesarean sections done at the Boston City Hospital for cephalopelvic disproportion.

300 BORDERLINE CASES

Normal	112
Low Forceps	138
Midforceps	20
High Forceps	3
Cesarean Sections	25
Versions	2
	<hr/>
	300

The borderline cases were those included in the categories previously mentioned as indications for x-ray pelvimetry. Two hundred and fifty, or 83 per cent, were delivered easily either normally or by low forceps. The 20 midforceps were mostly unrotated posterior heads or midtransverse arrests in which there was no progress after from two to six hours of second stage labor with signs of incipient fetal distress. There were two stillbirths in the midforceps group. There were three high forceps cases which were done because of fetal distress in cases showing an ample pelvis by x-ray and external pelvimetry. These cases were apparently associated with cervical dystocia, and there was one fetal death in the series. There were 25 cesarean sections in the x-rayed group which constituted all but four of the cesarean sections done in the three years, 1939 to 1942, for disproportion. The two internal podalic versions were done for signs of fetal distress with high heads with unruptured membranes and adequate pelvis. They resulted in living babies.

In the entire series of 300 cases there were but three fetal deaths and no maternal deaths.

CESAREAN SECTION STATISTICS

	1937	1938	1939	1940	1941
Deliveries	3,295	3,320	3,262	3,225	3,202
Total cesarean sections	135	142	88	83	91
Primiparas	1,005	1,046	998	915	950
Cesarean sections for dystocia in primiparas	21	31	10	9	10
Incidence in primiparas	1 in 48	1 in 38	1 in 99	1 in 100	1 in 95

The total number of cesarean sections has decreased markedly since our adoption of x-ray pelvimetry. The incidence of cesarean sections for cephalopelvic disproportion in primiparas has been reduced to one-half the former number without jeopardizing the mother or baby.

The analysis of the 29 cesarean sections done for cephalopelvic disproportion from 1939 to 1942 is as follows:

29 CESAREAN SECTIONS—1939-1942

HOURS OF LABOR	MEMBRANES INTACT	MORBIDITY	MEMBRANES RUPTURED	MORBIDITY
No labor	6	0	0	0
Under 12 hours	4	0	5	40%
Over 12 hours	9	22%	5	80%

All but four of the cases were x-rayed. The patients not measured by x-ray were too uncomfortable in labor to be moved to the x-ray department which is considerably removed from the maternity floor.

There were six cases done by election before labor started. These were done in the early part of our work but now all patients regardless of apparent dystocia are usually given some test of labor.

It is evident from the above chart that long labors followed by cesarean section especially if the membranes are ruptured are prone to increase the rate of morbidity. Our present policy in borderline cases with membranes intact is to allow twenty-four hours of pains with a frequency of five minutes or under as a test of labor. If the membranes are ruptured, a test of twelve hours is considered adequate. These criteria of course may be influenced considerably by maternal or fetal distress. If there is no apparent cephalopelvic disproportion by external pelvimetry and x-ray, the cause of the dystocia must be sought for in uterine atony or an unyielding cervix and the test of labor broadened accordingly.

All of the cesarean sections in this series were of the low transverse cervical type and there were no deaths.

Summary

1. A system of combined external and x-ray pelvimetry is suggested.
2. This method has reduced the incidence of cesarean section at the Boston City Hospital by 50 per cent with no increase in fetal or maternal mortality.
3. The technique is available to any practitioner and depends largely on clinical examinations.

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THE RELATION OF THE SACRAL PROMONTORY TO THE PELVIC INLET*

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THE anatomist William Turner more than a half century ago wrote, "With the exception of the skull, no portion of the skeleton presents greater individual variations than the pelvis." The truth of this statement has been made greatly manifest in our time, for through the use of roentgen methods has come the opportunity for the study of the bony pelvis on a far greater scale than was possible to our ancestors. The reason for such wide variation in this part of the skeleton must be sought in the fact that the pelvis is developed from a considerable number of bones and that during its growth to the adult state it is subjected to an indefinite number of nutritional, mechanical, and hormonal influences.

The present study is concerned with but one aspect of pelvic variation and that is the pelvic relationships of the upper sacrum, and in particular the position of the promontory of the sacrum in its relation to the plane of the pelvic inlet. In this investigation the roentgenologic findings in 200 primigravid women have been studied. These women were unselected and represent a group who were registered for delivery in the prenatal clinic of the New Haven Hospital during the year 1942.

It is because of the wide variation in position of the sacral promontory in its relation to the bony pelvic canal that some modern investigators have found that for clinical purposes it is necessary to abandon the idea that the superior strait, as described in anatomic texts, should be considered as the plane of the obstetric pelvic inlet. Therefore, from an obstetric point of view the plane of the pelvic inlet is considered to be bounded anteriorly by the upper posterior surface of the pubic symphysis and forward positions of the iliopectineal lines, laterally by the iliopectineal lines and posteriorly by the posterior portions of these lines and the anterior upper surface of the sacrum at the point where the convergence of these lines takes place. The importance of this plane in the mechanism of labor has been emphasized by Caldwell, Moloy and D'Esopo,¹ who state, "We believe that the promontory is too unstable in position to the plane of the inlet to be used as a point of origin of such an important obstetric diameter (the true conjugate diameter). This posterior point should be in the midline of the lower anterior sur-

*This study was made possible through grants from the Clinical Research and Teaching Funds of the Yale University School of Medicine.

face of the first sacral vertebra where the continuation of the iliopectineal lines on either side meet each other."

That a wide variation exists in the position of the promontory is seen in this study of its relation to the posterior end-point of the antero-posterior diameter of the plane of the pelvic inlet.

In these 200 cases the promontory rested at or near this point in 61 instances,

The promontory rested 1.0 cm. above this point in 30 instances,
 The promontory rested 1.5 cm. above this point in 41 instances,
 The promontory rested 2.0 cm. above this point in 51 instances,
 The promontory rested 2.5 cm. above this point in 12 instances,
 The promontory rested 3.0 cm. above this point in 5 instances.



Fig. 1.—Small brachypelvic type pelvis, anteroposterior 10.0 transverse 11.5. The promontory rests 2.5 cm. above the posterior end point of the true conjugate. The diagonal conjugate is 12.0 cm. from which it might be assumed that the true conjugate was 10.5 cm., an error which might be costly.

From this evidence it becomes apparent that the position of the forward edge of the sacral promontory is too unreliable to be considered as the posterior end of the true conjugate diameter, for in this series it was at or close to this point in but 30.5 per cent of cases (Fig. 1). It also becomes obvious that because of this positional variation the value of the diagonal conjugate diameter as an index of the true conjugate diameter may be very much questioned. It is generally stated that the true con-

jugate diameter may be estimated from the former by deducting 1.5 to 2.0 cm. according to the height and inclination of the symphysis pubis. Some texts omit the question of height and inclination and simply deduct 1.5 cm. for the true conjugate diameter.

The facts seem to be that the diagonal conjugate cannot be considered a reliable index to the true conjugate diameter and that in some cases information so obtained may be misleading (Fig. 2). In the present series this fact was emphasized by a comparison of Cases 21 and 54, which had identical diagonal conjugate diameters of 13.0 cm. and true conjugates of 11.9 and 10.5, respectively.



Fig. 2.—Small mesatipellic type pelvis, anteroposterior 10.4, transverse 11.4. The promontory rests 2.0 cm. above the posterior end point of the true conjugate. Roentgenogram shows a breech presentation in a primigravida. The diagonal conjugate is 13.0 cm. from which the true conjugate estimation of 11.5 gives an error of 1.1 cm.

In this series an attempt was made to find out if high positions of the promontory were associated with any particular pelvic grouping according to the division into dolichopellic, mesatipellic, brachypellic and platypellic types. In the series these groups were represented as follows:

Dolichopellic type	30 instances or 15%
Mesatipellic type	84 instances or 42%
Brachypellic type	77 instances or 38.5%
Platypellic type	9 instances or 4.5%

These findings correspond with the findings in 1,100 women previously published,² which were for these groups: 18.6 per cent, 45.9 per cent, 32.2 per cent, 3.2 per cent, respectively.

In the 61 pelves in which the promontory was at or less than 1 cm. above the pelvic inlet plane, the division was:

Dolichopellic type	8.2%
Mesatipellic type	37.7%
Brachypellic type	45.9%
Platypellic type	8.2%



Fig. 3.—The promontory is located near the posterior end point of the true conjugate diameter. In this position it may very definitely influence the descent and position of the fetal head in its engagement in the true pelvis.

In the 71 pelves in which the promontory was 1 cm. or more but less than 2 cm. above the pelvic inlet plane, the division was:

Dolichopellic type	21.1%
Mesatipellic type	38.0%
Brachypellic type	38.0%
Platypellic type	2.8%

In 68 pelves in which the promontory was 2 cm. or more above the pelvic inlet plane, the division was:

Dolichopellie type	14.7%
Mesatipellie type	50.0%
Brachypellie type	32.4%
Platypellie type	2.9%

From this analysis it is apparent that no definite conclusions may be drawn, and that the high promontory position is somewhat, if but slightly, associated with the dolichopellie and mesatipellie types of pelvis.

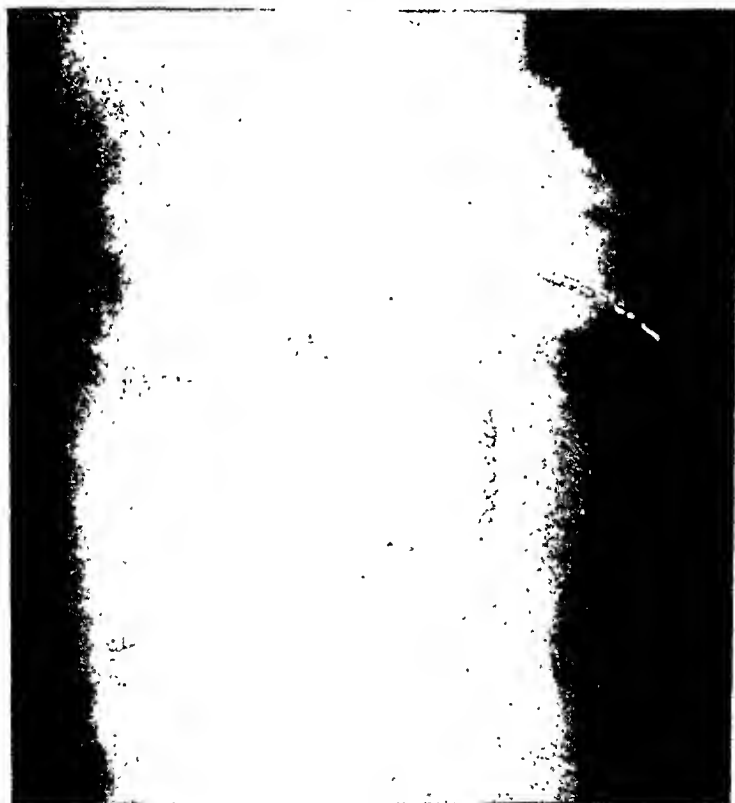


Fig. 4.—The promontory is located 3 cm. above the posterior end point of the true conjugate diameter. Its influence if any in the descent and position of the fetal head in its engagement in the true pelvis would not appear to be important.

In the present series also the reliability of the diagonal conjugate diameter as an index of the true conjugate diameter was determined. For this purpose 1.5 cm. was deducted from the diagonal conjugate and a leeway of 0.25 cm. + or - was allowed for the true conjugate. The result showed that the diagonal conjugate could be used as a satisfactory criterion in 76 instances, or but 38 per cent of cases.

Because of the variation in the position of the sacral promontory, it is apparent that the usual concept of the role played by this protuberance in the pelvic engagement of the fetus and in the mechanism of labor must be somewhat modified. Except in those instances where the promontory is at or near the posterior limits of the plane of the pelvic inlet it is difficult to see how in high positions it can play a very major part in the mechanism by which the fetal head settles into the pelvis. The fact is seen to advantage in Figs. 3 and 4. However, it should not be forgotten that in certain instances (probably rarely) even when the promontory occupies a somewhat high position it may project forward and the distance from the upper posterior symphysis to the promontory be less than that of the true conjugate diameter (Fig. 5).



Fig. 5.—Rarely when the promontory is located above the posterior end point of the true conjugate a forward position exists which makes the symphysis-promontory distance less than the true conjugate, in this instance 11.5 and 11.2 cm., respectively.

A question arises as to whether high positions of the sacral promontory are definitely associated with the so-called assimilation pelvis. There did not seem to be any direct evidence of this in the series, but it should be stated that the diagnosis of this type of pelvis from the single lateral roentgenogram cannot readily be made because all of the segments of the lumbar spine are not visible and in many instances the segmentational differences in the lower sacrum and coccyx are not easily distinguishable.

In conclusion, it may be stated that because of the variation in position of the sacral promontory the estimation of the true conjugate diameter based upon the length of the diagonal conjugate diameter is subject to error and pelvic capacity so determined should not be expressed in exact terms. In the present series the estimation of the true conjugate diameter based on the length of the diagonal conjugate was only approximately correct in 38 per cent of cases. Because of the variation in position of the sacral promontory the part played by this protuberance in the engagement of the fetal head may be either important or unimportant.

This study emphasizes again that roentgenologic methods are an important adjunct to the usual diagnostic obstetric procedures, for with the added knowledge that they furnish many of the mechanical problems of labor will be better understood and operative interference made a more intelligent procedure. In our own clinic the experience obtained by the routine use of roentgen pelvimetry in 2,000 primigravid women delivered during the past seven years confirms this opinion with increasing strength.

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THE EFFECT OF COMPLEMENTING THE DIET IN PREGNANCY WITH CALCIUM, PHOSPHORUS, IRON, AND VITAMINS A AND D*

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THERE have been a number of reports concerning the calcium, phosphorus, iron, nitrogen, and vitamin D requirements of the pregnant woman, but the actual number of patients studied is comparatively small. A series of metabolic studies were made by us as a part of an investigation of the therapeutic value of added amounts of calcium, phosphorus, iron, and vitamins A and D.

The patients were divided into four groups:

- (1) Control.
- (2) These patients received a proprietary cereal for its calcium, phosphorus, and iron content.

*Read at a meeting of the Chicago Gynecological Society, January 15, 1943.

This study was supported in part by a grant from Mead Johnson and Company, who also supplied the special cereal and vitamins.

- (3) These patients were given 39,900 international units of vitamin A and 5,550 international units of vitamin D daily.
- (4) These patients were given both the cereal and the vitamins.

Patients in the special groups were on the same medication throughout pregnancy. The average amount of the special cereal taken daily ranged from 30 to 50 Gm., but in the hospital the patients ingested approximately 100 Gm. (One hundred grams contained 0.78 Gm. calcium, 0.62 Gm. phosphorus, and 30 mg. of iron.)

The patients were hospitalized for a period of at least seven days and the diet and collection of excreta were continued throughout the hospital period. Balance studies were made over a five-day period, beginning thirty-six hours after admission. Our regular house diet was used in all cases, with oatmeal as the standard cereal, except in those patients receiving the special cereal, it was substituted for the oatmeal.

The data pertinent to each patient are summarized in Table I. Eleven of the 14 patients were primiparas because they, having no children, could be persuaded to spend the necessary periods in the hospital. The weight gain occurred during the period of observation, which is given in Table I. Eight patients gained excessively but only two developed toxemia. One pregnancy terminated in a premature delivery of a still-born fetus. There was nothing striking about the birth weights of the babies. All of the patients had breast milk but almost all had to use complementary feeding.

TABLE I. DATA CONCERNING THE SUBJECTS

NO.	AGE	GRAVIDA*	PARITY*	HEIGHT CM.	MINIMUM WEIGHT KG.	MINIMUM SURFACE AREA	WEIGHT GAIN KG.	WEIGHT BABY	NO. WEEKS AT DELIVERY	COMMENTS
1	18	i		151	32.5	1.24	17.0	2815	40	
2	18	ii	i	161	50.5	1.51	9.3	3165	40	
3	16	i		159	62.3	1.63				
4	21	i		151	58.6	1.53	16.9	3640	43	Toxemia
5	25	i		162	46.4	1.47	10.5	2945	38	
6	27	ii	i	158	67.0	1.67				
7	19	i		155	53.1	1.50	14.4	3610	40	
8	19	ii		162	49.4	1.50	13.8	3330	42	
9	22	i		155	51.5	1.48	10.9	3405	40	
10	20	i		158	57.5	1.58	14.1	2315	32	Toxemia Stillbirth
11	25	i		154	46.5	1.41	12.2	3300	39	
12	41	v	iii	153	60.2	1.56	6.4	3075	37	
13	24	i		163	57.4	1.60	16.3	3525	41	Postpartum hemorrhage; transfusion
14	18	i		159	56.5	1.57	13.5	4675	43	

*Gravida, number of pregnancies; parity, number of viable babies.

The intake for the various substances studied as well as the balances are given in Table II.

The calcium and phosphorus balances were positive in all 25 ante-partum periods. There were 8 post-partum periods. Only one patient had a negative balance. If the calcium and phosphorus secreted in the milk had been included, all balances after delivery would have been negative.

TABLE II. AVERAGE DAILY INTAKE AND BALANCE*

NO.	GESTATION OR PUER- PERIUM WEEKS	WEIGHT KG.	CALCIUM (GM.)		PHOSPHORUS (GM.)		NITROGEN (GM.)		IRON (MG.)	
			IN- TAKE	BAL.	IN- TAKE	BAL.	IN- TAKE	BAL.	IN- TAKE	BAL.
Group I										
1	15	32.5	1.330	0.625	1.525	0.525	11.23	2.85	14.84	8.77
	28	43.6	1.440	0.448	1.683	0.573	12.21	2.22	16.24	3.62
	38	49.0	1.434	0.336	1.673	0.633	12.13	2.44	16.15	7.33
	2 pp.	37.4	1.418	0.695	1.596	0.291	11.94	1.43	15.83	11.35
	6 pp.	41.0	1.409	0.495	1.545	0.555	11.73	3.20	13.57	5.56
2	25	54.6	0.702	0.148	0.932	-0.008	7.34	-2.37	13.39	4.89
	39	59.8	0.819	0.564	1.035	0.095	7.79	-1.16	11.46	5.46
3	19	62.0	1.441	0.331	1.751	0.861	12.61	3.11	17.47	10.37
Group II										
4	24	58.6	1.462	0.592	1.612	0.332	11.36	0.69	22.54	9.61
	34	67.0	1.637	0.497	1.726	0.436	11.87	1.10	24.21	15.53
	39	73.0	1.436	0.410	1.668	0.468	12.10	-1.64	16.02	-28.17
	2 pp.	62.0	1.229	0.826	1.458	0.248	10.66	0.87	13.75	9.99
	6 pp.	60.3	1.389	0.618	1.615	0.555	11.78	2.80	15.66	10.21
5	28	52.8	1.488	0.821	1.614	0.45	11.39	2.38	21.91	12.16
	2 pp.	46.6	1.543	0.539	1.668	0.358	11.50	1.54	21.76	12.15
6	26	67.0	1.481	0.811	1.615	0.735	11.47	2.83	20.96	10.06
Group III										
7	20	57.0	1.438	0.508	1.682	0.272	12.18	1.86	16.18	8.51
	30	63.7	1.412	0.402	1.649	0.309	11.92	0.79	15.95	0.43
	2 pp.	61.6	1.240	0.456	1.372	-0.458	9.79	-1.91	13.14	7.42
8	39	61.3	1.318	0.818	1.610	0.790	11.79	2.74	16.15	10.86
9	15	55.0	1.160	0.476	1.481	0.431	11.02	1.19	15.84	6.40
	30	61.5	1.440	0.430	1.684	0.524	12.18	3.88	16.24	7.57
	2 pp.	52.7	1.440	0.174	1.683	-0.797	12.21	-1.38	16.24	5.69
Group IV										
10	17	60.0	1.424	0.673	1.672	0.552	12.13	2.36	16.32	6.41
	30	71.6	1.442	0.621	1.685	0.725	12.19	0.92	16.28	6.92
11	16	47.2	1.628	0.331	1.733	0.403	12.07	0.43	23.63	4.75
	33	54.5	1.648	1.021	1.748	0.868	12.14	2.75	24.02	13.97
12	23	66.0	1.653	0.321	1.752	0.471	12.14	2.06	24.10	8.17
	38	62.0	1.454	0.171	1.466	-0.294	9.14	-1.85	20.39	-16.29
13	25	65.5	1.581	0.436	1.696	0.876	11.86	2.07	22.92	12.72
	40	73.8	1.410	1.068	1.558	0.896	11.10	3.59	19.37	12.37
14	18	58.0	1.657	-0.903	1.757	0.428	12.18	0.434	24.18	5.09

*The negative balances are indicated by a minus sign.

The articles published by Maey and Hunscher, and especially the extensive bulletin published by Coons and co-workers, summarize all data on metabolism in pregnancy published prior to 1935. These studies

indicated that an average intake of 1.320 Gm. of calcium resulted in a retention of 0.194 Gm. per day during the last three months of pregnancy. Likewise, an average daily intake of 1.713 Gm. of phosphorus resulted in a retention of 0.289 during the last three months of pregnancy. Our balances are, on the whole, in agreement with the ones previously reported. Individually and collectively, we can see no change in the metabolism of calcium or phosphorus in those patients who received added calcium or vitamins A and D. Our patients generally had slightly larger positive balances than the average figures reported by Coons.

Approximately one-half of the nitrogen balances compiled by Hunscher and associates indicated a retention of nitrogen of from 1 to 3 Gm. daily, with an average of 2.28 Gm. nitrogen. The retention per kilogram of body weight varied from 0.14 to 0.19 Gm. The average intake of 13.70 Gm. of nitrogen, based on Landsberg and Coons' data, indicated an average retention of 1.96 Gm. A nitrogen intake below 10 Gm. per day usually resulted in a negative balance.

Our data for the nitrogen metabolism are given in Table II. Only two patients had a negative balance during pregnancy.

Hunscher and co-workers found from their work and a survey of the literature that the maternal body retains a considerable excess of nitrogen during pregnancy beyond that required for the fetus and its adnexa. Following parturition there is a loss which persists over the first two weeks or more of the puerperium.

An interesting observation was made by Melnick and Cowgill, who found that when pregnant dogs were fed on protein-free diets at a high level of caloric intake and were subjected to their standardized plasmapheresis technique, it was possible to deplete the animal of its reserve serum protein and to reduce the serum protein concentration to the basal level (3.5 to 4.2 per cent necessary for the formation of edema) within less time than normal. Once the basal serum protein level is attained, the pregnant or lactating dog exhibits a marked impairment in its ability to regenerate serum protein. This inability to form serum protein may be due to the needs of the fetus or to faulty absorption by the mother.

There is an increased need for iron in pregnancy to take care of the increased blood volume and for the fetal demands for its own body development and also as a reserve for postnatal growth. The iron content of the newborn infant ranges from 0.266 to 0.937 Gm. The average daily transfer of iron from mother to fetus during the first two-thirds of pregnancy has been estimated to be 0.4 mg., and during the last third to be 4.7 mg. daily.

In one series, Coons and co-workers report an average intake of 14.72 mg., and a storage of 3.16. In another series, the intake ranged from 9.45 to 34.88, with an average of 15.74, and an average storage of 2.45 mg., with a range of from 0.23 to 6.88 mg. of iron daily. There were no

negative balances, but approximately 75 per cent of the studies were below that of the estimated fetal demand. They felt that the low retentions were not due to a low total iron intake, but probably to a deficiency or other dietary factors which promote the utilization of iron.

Coons also found that on comparable levels of iron intake in the usual diet, the retention by a group of southern women averaged almost 50 per cent lower than that for some Chicago women during corresponding periods of pregnancy. Coons also mentions that the quality, as well as the quantity, of iron intake, physiologic demands of pregnancy, and slight digestive upsets in pregnancy seem to be important factors in iron retention.

Toverud determined the iron balance in ten women in the last trimester of pregnancy. The daily intake varied from 7 to 28 mg. Two patients had a positive balance on an intake of 13 mg., and two had a negative balance on an intake of 15 mg.

Our data are given in Table II. Most of our patients showed a positive balance with an intake of iron ranging from 12 to 24 mg., with an average of 18.8 mg.; the retention ranged from a negative to a positive balance of 12.57 mg., with an average of 8.54 mg. One patient had a negative balance of 28.17 mg., with an intake of 16 mg.

We have listed in Table III the minimum, maximum, and average intake and balances per kilogram of body weight. The figures for the intake per kilogram for each subject tend to be more constant than the figures for the daily intake per subject. Since the weights are changing, this is of importance. Furthermore, the daily balances per kilogram indicate that although some patients are in positive balance, yet the amount retained per kilogram of body weight is far less than the average.

TABLE III. DAILY INTAKE AND BALANCE IN MG. PER KILO BODY WEIGHT DURING PREGNANCY

	CALCIUM			PHOSPHORUS			NITROGEN			IRON		
	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.	MIN.	MAX.	AV.
Intake	12.9	40.9	24.8	17.3	46.9	28.3	150.4	345.6	195.0	0.19	0.50	0.32
Retention	2.7	20.3	10.0	1.6	16.2	9.0	7.49	87.8	34.8	0.09	0.39	0.16

The numbers of patients in each group are too small for comparative purposes. However, other data were studied in groups containing 95 to 176 patients. Differences were present but either they were not significant or if significant the number of patients was too small.

Summary

Metabolic studies of calcium, phosphorus, nitrogen, and iron were made on 14 patients at intervals during pregnancy. Although the patients were given different diets, no significant changes were noted. The intake and retention of the substances studied were essentially similar to those reported in the literature.

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THREE CASES OF SULFATHIAZOLE TOXICITY IN OVER NINE HUNDRED WOMEN TREATED FOR CHRONIC GONORRHEA

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NINE hundred and four female patients with gonorrhea alone or with gonorrhea combined with syphilis were admitted to the venereal service of the Kingston Avenue Hospital during a period of eighteen months. All of these were admitted with positive gonorrheal cultures and of these, many had positive spreads. They were hospitalized for periods varying from two to four weeks at the request of the Health Department in order to control the spread of venereal disease.

Careful histories, physical examinations, and laboratory tests which included blood counts, sedimentation rates, and urinalyses were routine. The patients received dosages of sulfathiazole varying from 3 to 4 Gm. daily for from seven to ten days. Albuminuria, hematuria, anemia, and leucopenia were contraindications to the administration of the drug. Urine examinations and blood counts were done periodically during treatment. Our previous experience had taught us that blood levels of sulfathiazole were of slight significance, and we abandoned them except in toxic cases.

Marked toxic symptoms were noted in only three cases* in the entire group. Minor toxic symptoms (i.e., dizziness, slight nausea, headache, faintness, and mild and transient rashes) were present at times. The patients were confined to bed only if symptoms appeared.

The following three severe toxic cases were encountered:

CASE 1.—Miss J. A., white, aged 30 years, was admitted to the Kingston Avenue Hospital on July 11, 1942, because of a positive gonococcal culture and a four-plus Wassermann. At the age of thirteen she became aware that she had congenital syphilis and was treated occasionally with arsenic and bismuth. She had an appendectomy at fourteen years of age. At twenty-two, she was stabbed in the abdomen necessitating resection of two inches of intestine and was discharged after two weeks. Three years prior to admission the patient was at home six weeks with "a pelvic inflammation." Her menstrual history was negative. She denied pregnancies.

*Two of these cases need never have occurred had the patients disclosed pertinent details of their past histories. See conclusions.

Physical examination revealed Hutchinson's teeth, and two lower abdominal scars. Vaginal examination disclosed negative urethra, Skene, and Bartholin glands. The cervix was not eroded, but showed a moderate purulent discharge. The uterus was small, anterior, and mobile. Both tubes were thickened.

The urine examination was negative, blood count 72 per cent hemoglobin; 8,100 white blood cells; 55 per cent polymorphonuclears and 45 per cent lymphocytes. Sedimentation rate was 18 mm. in forty-five minutes.

She received 4 Gm. of sulfathiazole daily for five days. On the sixth day she had a flare-up of the adnexa inflammation with severe abdominal cramps. Examination revealed tenderness in both lower quadrants. The vaginal examination was negative except for tenderness in the fornices. The next day, abdominal pain continued and there was tenderness over both lower quadrants and over the kidney areas. She vomited sixteen ounces in the morning and twenty ounces in the afternoon. Between 7 A.M. and 9 A.M. she passed only 5 c.c. of urine and upon catheterization only 2 c.c. of bloody urine were obtained. The temperature was 99° F., pulse 84, blood pressure 120/80. The blood count was 4,000,000 red blood cells; hemoglobin 70 per cent; 9,000 white blood cells and polymorphonuclears 65 per cent. In the evening the temperature rose to 100° F., pulse 100, and respiration 20. The urine showed two-plus albumin, many red and white blood cells, and occasional sulfathiazole crystals. At 11 A.M., she received 500 c.c. of 10 per cent glucose in saline intravenously, and at 4 P.M. another 500 c.c. of 5 per cent glucose. At 4 P.M. she voided 5 c.c. of urine and upon catheterization an additional 2 c.c. was obtained. That evening 10 c.c. of urine was obtained by catheter. The next day, July 16, she passed 2 c.c. of urine and another ounce upon catheterization. Later in the day, she vomited 6 ounces of greenish fluid and voided 7 ounces of urine. Ureteral catheterization showed no block in either kidney and no crystals were obtained. The blood findings were 4,000,000 red blood cells, 72 per cent hemoglobin, 21,000 white blood cells, 79 per cent polymorphonuclears, and a trace of sulfathiazole in the blood. The blood chemistry showed nonprotein nitrogen 29 mg. per cent and blood sugar 98. The blood pressure was 140/95, temperature 102° F., and the pulse 96. The urine examination revealed two-plus albumin, many white and red blood cells. 700 c.c. of 10 per cent glucose were given intravenously twice daily. On July 17, the physical examination revealed tenderness over both lower quadrants and over both kidney regions, but much less than on the previous examination. The vaginal examination disclosed the left adnexa tender and about 8 cm. in diameter, and the right adnexa thickened and tender. She passed 4 ounces of urine which showed one-plus albumin and fewer white and red blood cells than previously. The patient went home on a release the next day.

Two days after the onset of toxicity we obtained the following additional history which no doubt would have contraindicated the administration of sulfathiazole. A sister told us the patient was a heavy drinker and imbibed about two quarts of liquor daily. She also informed us that the patient attempted suicide with bichloride of mercury about four years prior to admission. Upon obtaining this additional information, a diagnosis of nephrosis was made since ureteral catheterization showed no blockage with sulfathiazole crystals.

CASE 2.—Mrs. M. C., white, aged 29 years, was admitted to the Kingston Avenue Hospital on July 6, 1942, with a positive gonorrheal cul-

ture from the urethra and cervix. This case is particularly interesting because of the pathology to the liver which is very often affected by sulfa drugs. At the age of seventeen, she had a spinal fixation with a tibial graft for a bone tuberculous process. She denied pulmonary tuberculosis. The menses were normal. She suffered with a "bladder condition" prior to admission. She had one child five years ago which died a few hours after birth.

Physical examination revealed signs of tuberculosis in the left upper lobe, a scar over the lumbar vertebrae, and also over the left tibia. Pelvic examination showed a purulent discharge from the urethra, Skene's glands, and the cervix which was lacerated. The uterus was small, anteverted and pulled to the left by the enlarged adnexa.

X-ray showed a productive tuberculosis in the upper lobe of the left lung. Urine examination was negative. The blood findings were 74 per cent hemoglobin, 4,600 white blood cells, 60 per cent polymorphonuclears, and 40 per cent lymphocytes.

After receiving 4 Gm. of sulfathiazole daily for seven days, the patient complained of nausea and weakness. Three days later the patient developed jaundice and complained of weakness. The next day the icterus increased. The icteric index was 55. The van den Bergh test was positive direct, immediate. The blood chemistry showed non-protein nitrogen 27, and sugar 75. The blood count was 4,000,000 red blood cells, 82 per cent hemoglobin, 6,600 white blood cells, and 68 per cent polymorphonuclears. The sedimentation rate was 18 mm. in thirteen minutes. No sulfathiazole was found in the blood or urine. The urine was positive for bile and urobilinogen. The stools were clay colored.

The patient was given 50 c.c. of 50 per cent glucose intravenously; twice daily; 1 c.c. of vitamin "B" complex daily; a high carbohydrate and protein, and a low fat diet. Her condition remained unchanged for ten days when nausea diminished and jaundice lessened. The duodenal contents showed a trace of bile before and after magnesium sulfate. The blood chemistry revealed 142 mg. per cent of total cholesterol. The fragility test for red blood cells started at 0.40 per cent and was not complete at 0.28 per cent. Bile and urobilinogen were present in the urine. On July 30 the icteric index was 35 and stools were normal. On August 4 the jaundice was very mild, her general condition was improved and upon signing her release she was discharged.

A review of the facts in this case emphasizes the necessity for a thorough investigation of the past history. This patient had a toxemia of pregnancy with eclamptic seizures.

CASE 3.—Miss E. H., Negress, aged 21 years, was admitted to the Kingston Avenue Hospital on May 12, 1942, with a positive gonorrheal culture from the cervix and urethra.

The past history and physical examination were negative. Except for a purulent discharge from the cervix and urethra the pelvis was negative. The laboratory findings were: 3,600,000 red blood cells, 68 per cent hemoglobin, and 8,400 white blood cells. The urine was negative. The sedimentation rate was 18 mm. in thirty-five minutes.

On May 14, she was given 1 Gm. of sulfathiazole four times a day. Four days later she complained of pains in the lower abdomen and legs. The temperature was 102.2° F., pulse 114, and respiration 24. The lower abdomen was tender, but there was no rigidity. Pelvic examination was negative except for a purulent discharge from the cervix

and urethra. The sulfathiazole was stopped after she was given 18 Gm. in four and one-half days. The following day the tenderness and rigidity increased in the right lower quadrant; however, there was no rebound tenderness. The vaginal examination was negative and did not explain the cause of the pain and temperature of 104° F. The same afternoon she developed a headache and stiffness of the neck. The physical examination now revealed a reddened pharynx and conjunctiva. The lungs and heart were negative. The abdomen was soft and the tenderness was diminished. The sedimentation rate was 18 mm. in twenty-eight minutes. The blood count was 3,200,000 red blood cells, 63 per cent hemoglobin, and 6,000 white blood cells. Agglutination tests for typhoid and typhus were negative. The urine showed a faint trace of albumin. On the same day the patient was slightly lethargic, her throat red, tongue coated, abdomen tender and rigid in both lower quadrants. The signs were now more marked. The surgical consultation on the same day, with the same findings, attributed them to a pelvic inflammation. The next day, the stiffness of the neck and headache persisted though the abdominal signs subsided. The temperature was 97.8° F., pulse 120, and blood pressure 110/80. The following day, the condition improved with only slight tenderness in both lower quadrants. Urine examination showed a faint trace of albumin and many pus cells in a catheterized specimen. On May 22, the medical consultant made a diagnosis of a right lower pneumonia. The temperature, pulse, and respiration were normal. The following day, x-ray examination of the chest was negative for consolidation and infiltration. Because of the bizarre symptoms and varied diagnoses we felt that this most likely was a drug reaction. To prove this, we decided to repeat the drug cautiously. The next day, after having taken 60 gr. of sulfathiazole headache, dizziness, nausea, stiffness of the neck, and pain in both legs returned. The temperature rose to 102° F., and the pulse to 128. The drug was discontinued and fluids were forced. The blood count was 4,830,000 red blood cells, 77 per cent hemoglobin, and 8,900 white blood cells. No sulfathiazole was present in the blood. On June 3, the legs were still stiff and the temperature, pulse, and respiration were normal. The next day all symptoms and signs subsided and the patient was discharged on June 8.

Summary

1. In a total of 904 cases treated with sulfathiazole, three cases of serious toxicity developed.

2. The first patient after receiving 20 Gm. developed toxicity on the fifth day of treatment. The second patient developed signs after 28 Gm., which was upon completion of the therapy. The third patient became toxic after receiving 16 Gm. for four days.

3. A history of liver or kidney pathology, anemia, leucopenia, and previous sensitivity to sulfonamides are contraindications to the administration of the drug.

4. The fact that only 3 cases of severe toxicity developed in a series of over 900 patients treated shows that sulfathiazole is a safe drug to use in the dosage given. This conclusion is all the more valid since two of the cases of severe toxicity could have been avoided had a more thorough history been available.

We hereby express our thanks to Dr. E. A. Horowitz for including those patients which were on his service, and to M. C. Finkel, for assistance in preparing this paper.

THE EFFECT OF STILBESTROL ON PUERPERAL MORBIDITY AND LACTATION*

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IT IS well known that despite all preventive measures, a certain proportion of puerpera develops evidence of endometritis. Statistics vary from clinic to clinic, depending on the type of patient received and the frequency of temperature notation; but if the criteria of the joint Committee on Maternal Welfare are followed, the uncorrected morbidity in most clinics ranges between 7 and 12 per cent for white women, and possibly twice this for colored. In our own Clinic, which admits no normal multiparas to the ward service, and which receives a large number of referred complicated cases, the uncorrected morbidity for 1937 to 1940 was 10.7 per cent for white women and 20.4 per cent for the colored race, abdominal procedures being excluded. To be sure, the great number of these infections are mild and of short duration, but they nevertheless represent foci of infection from which grave types of extension may develop.

The possibility that some form of estrogenic therapy might reduce this puerperal morbidity has been suggested to the author by several facts. The well-known studies of Williams¹ demonstrated that with the exception of the placental site, the uterine cavity is completely lined with endometrium by the fourteenth post-partum day, or shortly thereafter, but the area previously occupied by the placenta does not entirely disappear until six or seven weeks following delivery. Since urinary estrogen^{2, 3} is low following parturition, and since endometrial regeneration does not begin until after the usual time for the onset of endometritis, it seemed conceivable that the administration of this hormone might bring about a more rapid regeneration of the endometrium than normally occurs, with beneficial effects on the incidence of infection. It also seemed that other established effects of estrogen, such as that of maintaining a good uterine blood supply,^{4, 5} increasing the tone of the myometrium,^{6, 7} and sensitizing the latter to oxytocics,⁸ might militate against the occurrence of endometritis.

In 1940, Connally, Dann, Reese and Donglass administered 5 mg. of stilbestrol daily to 200 puerperal women, with results which were reported in this JOURNAL.⁹ This series showed an extremely low morbidity rate, but as the group was somewhat small and rather inadequately controlled, the present continuation of that study was undertaken.

*The stilbestrol used in this study was furnished by the Abbott Laboratories.

Methods of Study

1. From Sept. 1, 1940, to May 31, 1941, every other patient delivered on the obstetric service of the Johns Hopkins Hospital received almost immediately postdelivery 5 mg. of stilbestrol in oil, by intramuscular injection. Each day thereafter, 5 mg. of stilbestrol were given orally, until the patient was discharged. Those patients delivered by cesarean section and those having abdominal operations during the puerperium (tubal ligations) were excluded from the study. Aside from the administration of stilbestrol the care given the two groups of patients was identical. Each mother in both the control and treated categories received one ampule of obstetrical pituitrin by the intramuscular route, following the second stage of labor, and one ampule of ergonovine, intramuscularly, immediately after delivery of the placenta. In addition, both groups were given 0.4 mg. of ergonovine by mouth, at four-hour intervals, until six doses had been administered. This was not repeated unless the patient became morbid. The criterion of morbidity employed was that of the Joint Committee on Maternal Welfare, namely, a rise of temperature to 100.4° F., on any two days of the puerperium (not necessarily successive), with the exception of the first twenty-four hours, temperature readings being made at 8, 12, 4, and 8 during the day and at midnight and 4 A.M., if the patient was awake.

2. During the twelve months' period from June 1, 1941, to May 31, 1942, the program of giving alternate patients stilbestrol was discontinued and a somewhat different method of study pursued. In the first two quarters of this interval no stilbestrol whatsoever was administered; during the third quarter, all patients delivered vaginally received the hormone post partum for nine days, and during the last quarter for three days.

3. Throughout the two-year investigation, every effort was made to carry on breast feeding as usual. Since most studies heretofore reported on the lactation-inhibiting effect of stilbestrol have been done on non-nursing mothers (that is, in conjunction with "drying-up" the breasts), it has seemed particularly worthwhile to observe the incidence and course of breast feeding in the present series in which maternal feeding was urged in all cases.

Results

The total number of patients studied in the first year of the investigation was 909, of which 442 fell into the stilbestrol group and 467 into the control. The results in regard to puerperal morbidity are shown in Table I. Since the incidence of febrile puerperiums in Negroes is much higher than in white women, the two races have been considered separately. Although the make-up of the control and stilbestrol groups was quite similar in respect to spontaneous deliveries, instrumentation, intra-partum infection, etc., the incidence of puerperal morbidity in the two groups was decidedly different: among Negroes the control series showed three times the morbidity of the stilbestrol group and in white women four times. The total morbidity of 5.6 per cent in the treated group, as against 20.1 per cent in the control series, would seem of definite significance.

The results of the second year's study are shown in Chart 1. In evaluating the figures for the first six months, during which no stilbestrol was administered, it should be noted that these percentages are compar-

able to those observed in the clinic in previous years when no stilbestrol was given. Thus, between 1937 and 1940 among 2,174 white patients the puerperal morbidity was 10.7 per cent, while among 2,319 colored women it was 20.4 per cent. With the resumption of stilbestrol administration in the second half of the year, a major reduction in puerperal morbidity occurred. During the three months, when it was administered to all patients for nine days, the morbidity among white women was 1.1 per cent and among the black, 5.2 per cent; during the last quarter of the year, when the administration of the hormone was curtailed to three days, the morbidity among the whites was 6.0 per cent and among the blacks 10.2 per cent.

The effect of stilbestrol on the ability of mothers to nurse their infants is shown in Table II and Chart 1. Although lactation in Negroes was found to be slightly superior to that in white women, the difference was not of sufficient degree to warrant separate consideration. Table II shows the results of the first year's experience in which stilbestrol exerted a markedly suppressing action on lactation even though attempts are made to carry out breast feeding as usual. Only 45.3 per cent of women in the stilbestrol series could nurse their infants in contrast to

TABLE I. SHOWING THE PUERPERAL MORBIDITY, AS WELL AS THE TYPE OF DELIVERY, IN 467 CONTROL CASES AND IN 442 ALTERNATE CASES IN WHICH STILBESTROL WAS ADMINISTERED POST PARTUM, 5 MG. DAILY (FIRST YEAR'S STUDY)

	COLORED PATIENTS		WHITE PATIENTS		TOTAL CONTROL	TOTAL STIL-BESTROL
	CONTROL	STIL-BESTROL	CONTROL	STIL-BESTROL		
Number of cases	235	217	232	225	467	442
Spontaneous deliveries	165	142	149	138	314	280
Low forceps	OA	60	55	63	106	123
	OT	5	5	7	10	8
	OP	10	5	9	15	15
Breech extraction	3	7	14	8	17	15
Version and extraction	1	1	4	0	5	1
Episiotomies	81	85	90	100	171	185
Intra-partum infection	8	8	9	9	17	17
Total number of morbid cases	61	18	33	7	94	25
Total morbidity in per cent	26.0	8.3	14.2	3.1	20.1	5.6

TABLE II. SHOWING THE EFFECT OF STILBESTROL ON LACTATION IN THE SAME GROUP OF CASES AS CITED IN TABLE I

	CONTROL CASES	STILBESTROL CASES
Total number infants	485	478
Number on breast feeding only	361	217
Per cent breast-fed only	74.4	45.3
Average birth weight of breast-fed infants in grams	3,248	3,238
Average weight loss of same in grams	178	249
Average birth weight of all infants	3,198	3,180
Average loss in weight of all infants	194	266
Infants below birth weight after ninth day	237	361
Per cent below birth weight after ninth day	48.9	75.6
Inanition fever	11	49
Per cent inanition fever	2.2	10.2

74.4 per cent in the control group; the average weight loss was much greater in the stilbestrol series; in the control group only 48.9 per cent of the babies had failed to regain their birth weight after the ninth day, but in the stilbestrol series 75.6 per cent had been unable to do so; the incidence of inanition fever was more than four times as high in the stilbestrol series. Chart 2 shows the results in respect to satisfactory lactation during the second year of study. Here it may be seen that during the quarter in which stilbestrol was given for nine days, only one infant in six could be breast fed. During the last quarter in which the hormone was administered only three days post partum, the reduction in the incidence of breast feeding was less marked but was still substantial.

Vomiting rarely occurred, a fact in keeping with the belief that pregnant and puerperal women are peculiarly tolerant of stilbestrol.^{10-12, 14}

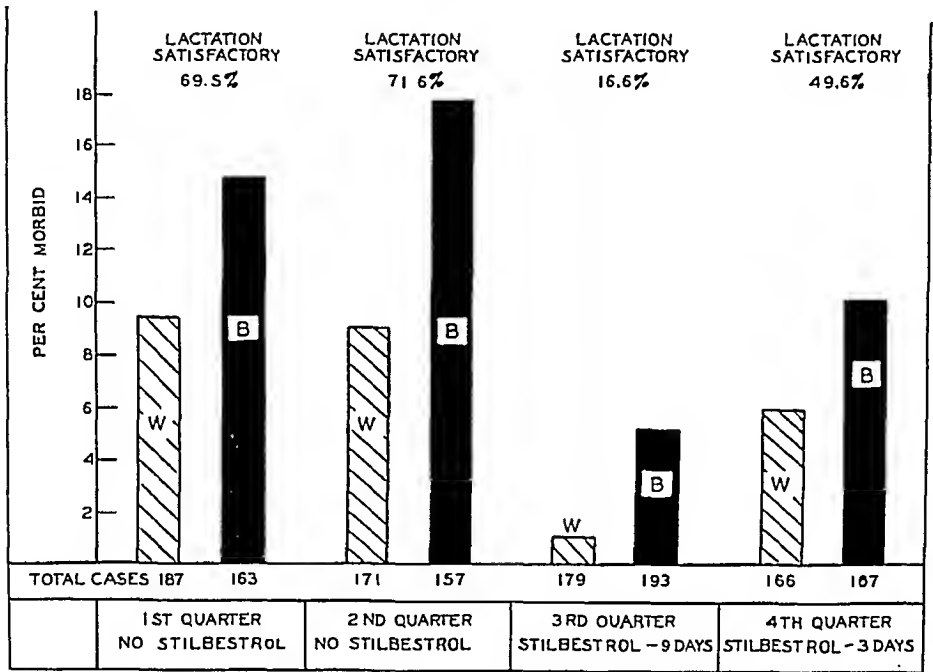


Fig. 1.—Showing the effect of stilbestrol on puerperal morbidity and lactation during the second year's study.

Comments

If it be true that the administration of stilbestrol in the puerperium reduces the incidence of febrility post partum, the observation would seem worthy of record as an endocrinologic fact. The mechanism by which stilbestrol exerts this effect is not clear but, as already indicated, the following possibilities may be speculated upon: (1) increase in uterine blood supply; (2) improvement in myometrial tone; (3) sensitization of the uterus to oxytocics; (4) increased rate of endometrial regeneration; (5) alteration of vaginal pH; suppression of mammary engorgement.

Concerning the effect of stilbestrol on the uterine blood supply, the well-known increase in vascularity of the pelvic organs prior to menstru-

ation and conversely, the ischemia which follows the menopause, attest the important role of the estrogens in this regard.

Markee's observations on the effect of estrogens on endometrial transplants likewise emphasize the action of these hormones in maintaining uterine blood supply. In 1938 Englehart⁸ reported three cases of puerperal endometritis treated with estrogens and attributed the beneficial results achieved to improvement in uterine vascularity and increased myometrial tone. Wolf,² as well as Falls, Laekner and Krohn,⁷ have shown that estrogens lend better tone to the post-partum uterus by increasing its contractility; while, in addition, Wolf observed that estrogens sensitize the myometrium to oxytocics. Very recently Rutherford¹⁵ has demonstrated that the administration of 10 mg. diethylstilbestrol daily to puerpera hastens endometrial regeneration by 25 per cent.

Although the effect of stilbestrol on puerperal morbidity, as shown in this paper, is an interesting endocrinologic fact, the associated inhibition of lactation precludes the routine employment of this measure. Indeed, in conclusion, the author wishes to stress the fact that he is *not recommending the use of stilbestrol in the puerperium*, but is merely citing additional evidence, of academic significance only, concerning the effect of this hormone on the post-partum course.

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UNIVERSAL EDEMA OF THE FETUS UNASSOCIATED WITH ERYTHROBLASTOSIS

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FETAL HYDROPS has been recognized for many years as a condition found in a small number of human fetuses which are dead at birth or die shortly thereafter. Ballantyne,¹ as early as 1892, was able to collect 65 cases from the literature and could find no uniformity in associated maternal complications or in pathologic conditions, other than the edema, in the affected fetuses. He states that "it is impossible to frame a satisfactory definition of this fetal malady for the cases which have been recorded by various authors present differences so wide as to suggest that we are dealing, not with a pathologic entity, but with a group of symptoms common to several different morbid conditions. It may, however, for convenience be defined as a rare condition of the fetus characterized by general anasarca, by the presence of fluid effusions in the peritoneal, pleural, and pericardial sacs, and usually by edema of the placenta; and resulting in the death of the fetus or infant before, during or immediately after birth. It is to be distinguished from such conditions as ascites, or peritonitis of the fetus, edema neonatorum, congenital elephantiasis and from fetal syphilis."

Certain of his cases are definitely recognizable as belonging to the entity subsequently recognized and designated as erythroblastosis. Of one such case he says, "the liver cells were imperfectly formed, and among them were many nucleated white blood cells; and whilst these latter were not, I think, so numerous as to constitute a lymphomatous state of the liver, still I have not seen so many leucocytes in the liver of a normal full-time infant. The same remarks apply to the microscopic examination of the spleen." Of another case he remarks that "nucleated white corpuscles were everywhere present . . . in the subcutaneous tissue were many lymphoid cells."

Not many of the infants described in this series of 65 were examined at autopsy, but among them are included three with congenital cardiac defects, two with polycystic kidneys, one with a diaphragmatic hernia, one with syphilis, one with simple degeneration of liver cells, and six in which leucemia or leucemoid reactions with great increase in cells in liver, spleen, and kidney are reported. The cells designated as leucocytes are doubtless nucleated red blood cells, and in the six exhibiting such cells, it may be considered that erythroblastosis was the probable

cause of the edema. Many of the other infants, however, in all probability did not have erythroblastosis.

In the years which have followed the publication of Ballantyne's monograph, the abnormal cells in the spleen and liver have been recognized as normoblasts and erythroblasts, and the condition in which they are found associated with severe generalized edema, has been linked with certain cases of icterus gravis in which similar abnormal cells are recognized. These two clinical pictures have been included under the name erythroblastosis, and during the last fifteen years over two hundred papers have been written on the subject.

In many of these papers one finds the statement that only certain cases of icterus gravis should be diagnosed as erythroblastosis since severe jaundice may be produced by septicemia, syphilis, atresia of the bile ducts, and other conditions. Almost never, however, is there mention of the fact that there are certain cases of universal edema of the fetus which should not be included in this category. Practically all authors appear to accept all hydropic infants as suffering from erythroblastosis.

This is one of the principal reasons for the commonly found statement that infants with erythroblastosis fail to show any picture which is histologically characteristic, despite the fact that the histologic pathology was one of the principal reasons for originally combining fetal hydrops and icterus gravis as a single entity. There are some authors, however, who believe that certain histologic evidence must be present in order to make a diagnosis of erythroblastosis, and that, in the absence of these findings, the diagnosis of erythroblastosis cannot be established.

I believe that the latter view is correct and that the diagnosis of erythroblastosis should be limited to that group of infants who appear to suffer from a specific disease entity. I also believe, with Ballantyne, that fetal hydrops is not a specific disease, but only a symptom common to several different morbid conditions.

Erythroblastosis should not be diagnosed unless all of the following symptoms are present: anemia, abnormal increase in nucleated red blood cells in the peripheral blood, erythropoiesis in locations where it does not normally occur, and enlargement of the spleen. In practically all infants with this disease other abnormal findings will also be present, but without those listed above the diagnosis is always open to question. Since in infants who survive, histologic examination of the organs is impossible, the diagnosis must rest on examination of the blood and palpation of the spleen.

Neither edema nor jaundice is essential for a diagnosis of erythroblastosis but in all, except in rare instances, some degree of one or the other, and often both, is present. In infants who die soon after birth, either one may be so mild as to go unnoticed. Associated conditions

which are usually but not invariably found are mild cardiac hypertrophy, mild decrease in thymic size, marked hypertrophy of the liver, bile thrombi in the intrahepatic ducts or bile pigment or hemosiderin in the hepatic cells or Kupfer cells (irrespective of the presence of visible external jaundice). In the hydropic group, pleural and peritoneal effusions and hypertrophy of the placenta are usually present.

Clinical Material

During the course of the last several years the possibility of the existence of erythroblastosis has been considered in over 100 infants who have been subjected to postmortem examination in the laboratories of The Chicago Lying-in Hospital. This has been either in relation to clinical findings such as an abnormal blood picture, edema or jaundice, or in relation to certain abnormal conditions found at necropsy. The diagnosis of erythroblastosis has been established with a fair degree of certainty in over 50 infants; in the remainder the condition was believed not to exist.

Among those in whom the typical findings of erythroblastosis were absent, there are 17 infants with the severe edema which is characteristically described as fetal hydrops. These infants comprise a fairly uniform group and appear to be an entity entirely separate from erythroblastosis. The majority of these infants have extreme pleural and peritoneal effusions which are usually greatly in excess of amounts found in erythroblastosis. These accumulations of fluid appear to develop very early in fetal life and often produce compression of both the thoracic and abdominal viscera. The organs are frequently hypoplastic in relation to the body size even after allowance is made for the increased weight due to edema. The lungs are usually especially small.

In contrast to erythroblastosis, the spleen and liver are never enlarged and the spleen is often extremely hypoplastic. The circulating blood shows little or no increase in nucleated red blood cells and abnormal erythropoiesis is rarely visible in any organ.

The histologic appearance of the tissues shows little variation from the normal. In those instances in which the lungs are hypoplastic, the alveoli are correspondingly immature; capillary ingrowth into the alveolar wall is retarded and the original cuboidal cells lining the alveoli are proportionately more numerous than normal for the gestational age. Although the spleen is often hypoplastic, Malpighian corpuscles are well developed. This is in contrast to the findings in erythroblastosis; in this condition the lymphoid tissue of the Malpighian corpuscles is greatly reduced in amount or is entirely absent. The liver does not show the presence of pigment in the bile capillaries or hepatic cells.

Four of the infants in this group of 17 were malformed; one had a cardiac abnormality consisting of a patent atrioventricular ostium, one had multiple malformations which included a harelip, cleft palate, left diaphragmatic hernia and hypertrophy of the clitoris; one had multiple malformations the most important of which were atresia of the trachea and polycystic kidneys, and one had only a hypospadias. Two infants were twins, and although the other of each pair also died they were not edematous and the cause of death appeared to be prematurity in each case. None of our infants with erythroblastosis have been malformed.

The maternal histories show many differences from those usually found in association with erythroblastosis. With one exception (and the possibility of one other in whom record is not available) the mothers are all under 30; six are primigravidas, a condition which we have not observed (except once in a patient with numerous previous transfusions) in erythroblastosis. We have been able to acquire information concerning subsequent pregnancies in 11 of the 17 women. Five have not had further pregnancies; six have given birth to seven normal living children. There have been no subsequent unfruitful pregnancies. This is in contrast to the group with erythroblastosis; among these, 15 are known to have had subsequent pregnancies; all, with one exception, ended in the delivery of infants with fatal erythroblastosis. This one infant was jaundiced at birth but survived after receiving three transfusions.

Of especial interest are the results of the Rh determinations performed on the mothers' blood. Blood could not be obtained from six patients, but of the 11 tested *all were Rh+*. These findings are in marked contrast to those in erythroblastosis; in that condition 90 per cent of 60 patients giving birth to babies with proved erythroblastosis whose bloods were tested in the same laboratory were Rh-.

The differentiation of infants with true erythroblastosis from those who suffer from some other pathologic condition is extremely important. The discovery of the Rh factor has greatly stimulated interest in erythroblastosis and the diagnosis is being made with much greater frequency than formerly. The recognition of erythroblastosis is most desirable, but it is equally important that the diagnosis be limited to those infants who actually exhibit the characteristic pathologic picture.

The prognosis for the future bearing of normal children is very poor after a woman once gives birth to an infant with erythroblastosis. Further attempts at childbearing are in general to be discouraged, but one should be certain that the condition exists before a recommendation against future pregnancies is made. Curtailment of pregnancy because of an erroneous diagnosis produces unnecessary unhappiness in women desirous of having children. For this reason, if for no other, it should be realized that erythroblastosis exhibits a specific clinical and pathologic picture, and that both severe jaundice and generalized edema may exist in conditions other than erythroblastosis.

Summary

Marked edema of the infant may exist independently of erythroblastosis.

There appears to be a characteristic clinical and pathologic picture consisting of extreme anasarca and extreme pleural and peritoneal effusions often associated with marked hypoplasia of the lungs and spleen. There is no increase in the number of circulating immature erythrocytes and ectopic areas of erythropoiesis are absent.

The mothers are often primigravidas and all of those so far tested are Rh+.

The condition should be definitely separated from erythroblastosis because of the difference in prognosis for future pregnancies in the two diseases.

It has been observed in one infant of two pairs of twins, the other twin in each case appearing normal except for prematurity.

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ACUTE INTESTINAL OBSTRUCTION DUE TO BANDS COMPLICATING PREGNANCY*

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THE objects of this presentation are to direct attention to the serious combination of acute intestinal obstruction and pregnancy, largely because of delay in diagnosis; to outline the proper management of such cases based upon personal experience and to review the literature; and to report two cases of our own, in one of which two episodes of intestinal obstruction occurred during the same pregnancy. We have found no previous report of a similar case.

Acute intestinal obstruction has always been a serious disease but when it is complicated by pregnancy, several new factors appear which test one's judgment, particularly with regard to the diagnosis and treatment. The incidence of acute intestinal obstruction during pregnancy is not frequent. At the Woman's Hospital in New York, Bemis³ found 2 instances among 15,000 obstetric cases, while at the Boston Lying-in Hospital from 1916 to 1938, Smith and Bartlett⁴ found that among 66,431 deliveries, there were 61 abdominal complications only one of which was an intestinal obstruction. In an extensive review of the literature, Slemons and Williams⁵ found that any of the causes of intestinal obstruction in the nonpregnant individual may complicate pregnancy but the most common cause is postoperative bands, between 200 and 300 such cases having been reported, the previous operation usually having been for organic pelvic disease or for removal of the appendix. They found that ileus during pregnancy was accompanied by a maternal mortality of 40 per cent and a fetal mortality of 65 per cent, the highest death rate occurring with intussusception and the lowest when the obstruction was due to a constricting band. That some progress has been made in the handling of this condition is shown by the report of Eliason and Erb,⁶ who quote a series of 95 cases of all types collected by Ludwig up to 1913 with 54 per cent mortality, a series of 80 cases collected by Mikulicz-Radecki from 1913 to 1925 with 39 per cent mortality and then present their own collected series of 66 cases from 1925 to 1935 with 21 per cent mortality. All of these series show that adhesions and

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volvulus are the most frequent causative agents while strangulated hernia is seldom the cause, since the enlarged uterus pushes the intestine upward away from the hernial orifices.

Several authors have stated that there are three periods during pregnancy when obstruction is most likely to occur: (1) during the fourth and fifth months when the uterus ascends from the pelvis, (2) during the eighth and ninth months when the fetal head descends into the pelvis, and (3) during delivery and the early days of the puerperium when a marked change occurs in the size of the uterus with consequent change in intra-abdominal pressure. This oft-repeated statement should not be taken too seriously, however, since Hansen⁷ has analyzed a series of 80 cases with respect to the time during pregnancy when obstruction occurred and found them distributed generally during pregnancy after the third month, the actual figures being 22.5 per cent in the ninth month, 17.5 per cent in the eighth, 16.25 per cent in the seventh, 11.25 per cent in the sixth, 13.75 per cent in the fifth, 3.75 per cent in the fourth, 5 per cent in the third, 8.75 per cent post partum, and 1.25 per cent in labor.

Having reviewed the American literature of the past ten years we note that most articles consist of case reports only and therefore we believe that a survey of these cases together with two cases of our own and a summary of the experience in 33 Philadelphia hospitals will be of interest at this time. While any cause of intestinal obstruction may be associated with pregnancy, we are concerned primarily with the type that is due to bands resulting from a previous abdominal or pelvic operation. We have found that the cases reported during the past ten years have occurred in almost equal numbers after simple appendectomy and operations upon the adnexa and in one case following a cesarean operation. They have occurred after any type of incision, including the McBurney, and in most of the cases no drainage had been used at the primary operation. The time interval between an operation and a subsequent obstruction varied considerably, the earliest obstruction occurring eight weeks after a previous operation. Of particular interest is the fact that in cases reported by Barone, Power and Kuhn,² Casagrande,⁵ Weintraub and Jaffe,¹⁰ as well as in one of our own cases, the patient had gone through a normal pregnancy between the time of the original operation and the pregnancy which became complicated by obstruction. We have found only 13 cases of obstruction due to bands reported during the past ten years. In three cases the mother died and the fetus was lost in three.

Under the auspices of the Committee on Maternal Welfare of the Philadelphia County Medical Society a request was sent to 50 Philadelphia hospitals that a search be made through their records of the preceding ten years. Thirty-three hospitals replied and using the information received together with cases gleaned from the records of the Philadelphia County Medical Society, a total of 22 cases of intestinal obstruction complicating pregnancy was found, of which 12 were ante partum.

Of these, seven were due to bands or adhesions resulting from a previous operation, death of the mother resulting in five instances and death of the fetus in six. In only one instance therefore did the pregnancy result in a living child. Obstruction followed a previous appendectomy in three instances, an appendectomy and pelvic operation in two, and an upper abdominal operation in one. In one case there was a pelvic operation without appendectomy. Obstruction occurred between the third and seventh months in all except one case in which it occurred at term. While the results in this Philadelphia series are much worse than those from the literature, none of them had been previously reported, and it should be remembered that one is more likely to report successful results than poor ones. Were it possible to get similar statistics from the country at large, it is quite likely that the results would be much worse than the reported statistics. Table I summarizes the situation as we have found it.

TABLE I. OBSTRUCTION DUE TO BANDS DURING PREGNANCY. (1932-1941)

	REPORTED IN LITERATURE	PHILADELPHIA HOSPITALS	PERSONAL CASES
Number of cases	13	7	3*
Death of mother	3	5	0
Death of fetus	3	6	1†

*Two obstructions occurred in one patient.

†Neonatal death; prematurity, immaturity, intracranial hemorrhage.

Our own experience with this condition is outlined in the following case reports:

CASE 1.—A 23-year-old white female was admitted to the Jewish Hospital on Aug. 21, 1941, complaining of cramplike epigastric pain of three days' duration, nausea and vomiting on two occasions, and during the preceding twelve hours had been obstipated. She was six months pregnant, the fetus being active and the fetal heart sounds well heard. She had been operated upon in November, 1940, for removal of the appendix and resection of an ovary. On the day before admission her habitual mild constipation seemed more marked but responded to a laxative and an enema. On the day of admission the pain was more severe and an enema was ineffectual although she passed a small amount of flatus. At this time she was quite uncomfortable on account of abdominal cramps, the temperature was 99° F., pulse 90, and respirations 20.

Urine examination was negative except for a plus 4 acetone. The hemoglobin was 86 per cent, leucocytes, 5,600, with 56 per cent polynuclear cells. The general physical examination was negative except the abdomen, which was slightly distended and tender with muscular rigidity over the upper portion. The uterus was enlarged to a size corresponding to a six months' pregnancy and peristalsis was heard, almost normal in character, over the upper abdomen and in both loins. On the following morning the symptoms persisted, the abdomen was more distended, and peristalsis was less evident. A flat x-ray film showed definite evidence of distended loops of small bowel in the right lower quadrant and laparotomy was performed about twenty hours

after admission. The obstruction was found to be in the lower ileum and was due to five bands, four of which were running from the lower ileum to the pelvis and the other was running from the ileum to the descending colon. These bands were divided and ligated and a prophylactic ileostomy was done proximal to the highest point of obstruction, since the bowel was moderately distended. After operation the patient was given morphine and progesterone to prevent uterine contractions and prostigmine to stimulate intestinal activity so that the distended loops would be less likely to adhere to each other and cause a secondary obstruction. Her convalescence was uneventful and she was discharged on the fifteenth day after operation, the ileostomy having closed and the pregnancy continuing normally.

On Nov. 21, 1941, at 1:00 A.M. she was again admitted to the hospital with some abdominal pain and vomiting, although she had had three bowel movements during the preceding day. She was treated conservatively during the night and was comparatively comfortable the next morning. She passed no flatus and later in the day her pain recurred with increasing severity, was intermittent in character and she again vomited. A flat x-ray film disclosed distended loops in the ileocecal region and the conclusion was reached that she was again obstructed. Although she was entering her last month of pregnancy, the head was still floating, and it was decided that the induction of labor would necessitate undue delay before the obstruction could be relieved. Accordingly she was submitted to laparotomy. On opening the abdomen many loops of distended intestine were found above and to the right of the enlarged uterus which were adherent to the right abdominal wall. A classical cesarean section was done by Dr. Jacob Walker, obtaining a living but premature male child weighing 5 pounds. After the uterine incision had been sutured, with of course marked reduction in the size of the uterus, the abdomen could be more readily explored. Numerous adhesions between loops of small bowel and between the small bowel and the right abdominal wall were found and divided until it was evident that all points of obstruction had been relieved and the abdomen was closed without drainage. The baby died the following morning and necropsy revealed intracranial hemorrhage. The mother's convalescence was uneventful.

CASE 2.—A 31-year-old white female was admitted to the Jewish hospital at 10 P.M. on Jan. 25, 1942, with a history of pain in the right side of the abdomen and repeated vomiting during the preceding twenty-four hours. Fifteen years previously she had been operated upon for a ruptured appendix and the wound had drained for a long time. A hernia appeared in the incision nine years ago. Since then there was an occasional throbbing in this region but the hernia was always reducible until the onset of the present attack. She had had one bowel movement in the morning but had passed no flatus since. She was in her sixth month of pregnancy which had been progressing normally. She had had two children since her operation, at eleven and nine years, respectively, before her present admission. On examination there was a tense incisional hernia in the lower right side of the abdomen, peristalsis was hyperactive, the temperature was normal, and the pulse was 104. She was still vomiting and quite apprehensive. As the result of our experience with Case 1 it was decided to operate immediately. The old scar was excised exposing a large hernial sac which was filled with adherent omentum. At first it was thought that this omentum by

angulating the transverse colon might be causing the obstruction. However, after the omentum was freed and replaced in the abdomen, examination of the right lower quadrant revealed two separate peritoneal bands, running from the terminal ileum to the parietal peritoneum below the incision. These bands were angulating and obstructing the small bowel. They were cut and the bowel released and the abdomen was closed without drainage. Postoperatively there was a slight reaction for the first day and she had a Wangenstein suction drainage applied for two days. On the fourth day she developed cramplike pain suggestive of a threatened miscarriage, but this subsided after the use of morphine. Her further convalescence was uncomplicated, and she was discharged on Feb. 6, 1942, with the pregnancy continuing normally.

Comment

The diagnosis of intestinal obstruction during pregnancy should not be difficult, but it is seldom made in the early stage. The symptoms of obstruction are pain, vomiting, constipation, and distention, in that order of frequency, but it will be readily noted that any or all of these symptoms may be present in the course of a normal pregnancy. Rhythmic pain may be equally prominent in an oncoming miscarriage as well as in intestinal obstruction, but in the former it is not likely to be associated with the other cardinal symptoms of obstruction and is often accompanied by some bloody vaginal discharge. Vomiting is, of course, quite common in early pregnancy but most obstructions occur after the fifth month when emesis is not to be expected. However, in one case reported the vomiting continued all through pregnancy up to the time that intestinal obstruction supervened, while in another case there was no vomiting at any time. Constipation and distention are so common during pregnancy that they are of little value in differential diagnosis but the presence of high-pitched tinkling peristalsis on abdominal auscultation may be of considerable aid in the obstructed case. Many cases give a history of minor obstructive symptoms during pregnancy before complete obstruction occurs. The demonstration of small bowel distention by x-ray examination is almost pathognomonic of obstruction but a negative report does not rule out the condition. The diagnosis will be made with increasing frequency provided the obstetrician thinks of this possibility in all pregnant patients who have had a lower abdominal operation, whose complaints are of more than a minor character which are not promptly relieved by minor therapy.

In a condition as infrequent as this, it is obvious that no obstetrician has had an extensive experience in its management and we must be guided by the collective opinions of those who have been confronted by this serious complication. Weintraub and Jaffe¹⁰ offer the alliterative aphorism that pregnancy predicates pernicious procrastination in the management of this condition and they believe that until proved otherwise each case is a *prima facie* one of mechanical obstruction. In corrob-

oration of this they have presented 4 cases and the only fatality was in a patient not operated upon. Blair⁴ divides obstruction during pregnancy into two classes: (1) those without a past history of intestinal or peritoneal trouble, and (2) those with a history of peritoneal trouble with possible operation. In either type he advocates opening the abdomen. If the case belongs to Class 2, he states that the condition causing the obstruction should be dealt with, ignoring the pregnancy; if the case belongs to Class 1, he advises emptying the uterus by hysterotomy as in these cases obstruction is usually due to pressure of the enlarged uterus on the sigmoid as it enters the pelvis. Slemmons and Williams⁸ state that surgical consultation is essential. They believe that there are no inflexible rules for handling the pregnancy since so many variable factors enter the field, such as the period of gestation, the type of obstruction, the intensity of the toxemia, the strength of the woman, and the likelihood of delivery before long. They state that evacuation of an advanced pregnancy, occasionally even hysterectomy, may be necessary to secure proper exposure of the pelvis. If hysterotomy is to be done, it should precede any operation on the bowel in order to avoid contamination of the uterine wound.

Discussion

In our first case the use of conservative intestinal intubation was considered before operation but was fortunately rejected since it could not have relieved more than the first point of obstruction and the patient, having five points of angulation would have been left with several closed loops beyond. Moreover the obstruction in these cases is due to the fact that the enlarging uterus pushes the small bowel toward the upper abdomen making tense bow strings of adhesive bands which ordinarily might give no trouble. So long as the uterus enlarges it is difficult to see how the progressive angulation could be relieved by intubation. In an extensive consideration of intestinal obstruction from both the clinical and experimental aspects, Aird¹ states that he has been impressed by more than one case of adhesive obstruction, treated by suction drainage and saline infusion for twenty-four hours or more, only to present at operation a strangulated and devitalized bowel. The twenty-four hours of delay may mean the difference between viability and gangrene. It is conceivable to him that while the present vogue for prolonged preoperative decompression and saline administration may be expected to reduce the mortality of simple intestinal occlusion, it may actually lead to an increase in the mortality of intestinal strangulation. Even in simple occlusion of the bowel, patients still die with sufficient frequency to make him feel that we have yet something to learn of the lethal mechanism of the disease.

In our second case it might have been logical to assume that the incarcerated omentum in the incisional hernia caused obstruction by its trac-

tion on the transverse colon. Had the operation been terminated after the release of the omentum the patient would not have been relieved. The obstruction was in the lower small bowel due to bands which were found only, after the omentum was replaced, within the abdomen. This demonstrates the importance of a thorough search for multiple factors in such cases and undoubtedly our experience in the first case guided us in the operative management of the second.

Summary and Conclusions

Acute intestinal obstruction is an uncommon but serious complication of pregnancy. One of the most common causes of obstruction during pregnancy is the presence of adhesive bands resulting from a previous lower abdominal operation which become tant as the enlarging uterus pushes the intestine into the upper abdomen. Obstruction may occur at any interval after an abdominal operation and the fact that a patient goes through a normal pregnancy after such an operation is no assurance that she will not become obstructed during a subsequent pregnancy. The presence of mechanical obstruction should be suspected in any pregnant patient who has had a previous lower abdominal operation and who presents the obstructive triad of cramplike pain, vomiting, and obstipation. If x-ray examination shows distended small bowel the diagnosis is made, but negative x-ray examination does not rule out the diagnosis. The proper management of this condition consists of early operation to release the obstructing bands, making a thorough search until all points of obstruction have been released. Conservative intestinal intubation should not be used in this condition. Two cases have been presented in one of which two separate episodes of intestinal obstruction occurred during the same pregnancy.

We wish to thank Miss Malkiel, Secretary to the Maternal Welfare Committee of the Philadelphia County Medical Society and the various hospitals whose cooperation greatly assisted in the preparation of this paper.

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Discussion

DR. J. WALKER.—It is important for the obstetrician to realize that intestinal obstruction, although a rare complication of pregnancy, carries a high degree of risk for both the pregnant woman and the fetus. Much of this increased risk is un-

doubtedly due to the difficulty of early diagnosis, since, as the authors have indicated, the signs and symptoms of intestinal obstruction, distention, vomiting, abdominal pain and constipation, are commonly encountered during pregnancy as functional states, and the obstetrician is thus prone to ignore them until the picture of obstruction is dangerously well developed.

The incidence of this complication is quite low, being variously quoted as 1:15,000 to 1:68,000 cases. In my own experience, embracing over 8,000 private patients, I have encountered only two cases. The first patient was a 25-year-old primigravida who had a spontaneous rupture of the membranes at term, without labor pains. Thirty-five hours later uterine contractions began, and the physician ordered an x-ray examination, multiple pregnancy being suspected. The x-ray revealed a single term fetus, breech presenting. The pelvis was platypelloid with a true conjugate of 9 cm. I was called in consultation and performed a cervical cesarean section (Kroenig) six hours after the onset of labor, membranes having been ruptured for forty-one hours. The patient had an apparently normal postoperative course for three days, whereupon mild upper abdominal distention with high-pitched tinkling peristalsis began to appear. Although intermittently relieved, by gastric lavage, this was progressive. On the sixth postoperative day, distention was well marked. Dr. W. O. Abbott was called in consultation, and after unsuccessful efforts to pass the double-lumen tube, he advised operative relief of the distention rather than further delay. Barium enema had demonstrated obstruction at the sigmoid flexure, with distention above this point. Dr. Rothschild performed a transverse colostomy, and four days later, the fourteenth post-partum day, the patient's condition permitted abdominal exploration. An inflammatory process involving the posterior surface of the left broad ligament, posterior surface of the uterus, rectum, and sigmoid was found, and as the sigmoid was freed, a small amount of pus was evacuated. This procedure relieved the obstruction, and five days later closure of the transverse colostomy was carried out. Following a stormy convalescence the patient was discharged recovered, approximately seven weeks after the cesarean section. My second case was one of those described by Dr. Block.

What lesson are we to learn from this study? It does teach us to suspect intestinal obstruction when the abdomen bears a scar, with or without a history suggesting intermittent partial obstruction. Furthermore, this and other surgical complications of pregnancy warn us that the obstetrician should have had basic training in the handling of surgical problems; that he should remember that the enteric cavity contains more than a uterus and fetus, and that he should not hesitate to call for the aid of an experienced surgeon when signs or symptoms of a bowel lesion appear.

Binet, L., and Strumza, M.-V: Contributions to the Study of Shock, *Presse méd.* 48: 825, 1940.

The writers, using 64 dogs, produced variable grades of shock by giving the animals intravenous histamine bichlorhydrate (2.5 mg. per kg. body weight). They recorded then the blood chemistry, the kymographic tracings of blood pressure, and the hematologic findings in these animals.

They conclude that serious shock is primarily a condition requiring urgent hydration as a therapeutic measure. The results they obtained in the animals suggest that, in the milder cases of shock, saline, sodium bicarbonate and hypsulphite solutions were satisfactory while the more serious cases gave promise of better results when diluted blood was used. Of interest was the observation upon the use of propionylcholine perchlorate in the treatment; in animals, return from histamine shock was usually effected in two or three hours. The dosage of this drug was 3 mg. per kg. administered very slowly, by the intravenous route.

CLAIR E. FOLSOME.

DIAPHRAGMATIC HERNIA AS A CAUSE OF "INTRACTABLE HEARTBURN" OF PREGNANCY

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THE surprising incidence, or rather, the greatly increased frequency of diagnosis, of diaphragmatic hernia in the past two decades has occasioned a large number of papers on the general subject.¹ Those roentgenologists who have become "diaphragmatic hernia minded" have been able to solve many a knotty diagnostic problem by the demonstration of such a hernia. Obscure symptoms referable to the gastrointestinal tract, the biliary system or the cardiorespiratory system have disappeared following surgical repair of anatomic defects in the diaphragm. It has been estimated² that under conditions of general practice, symptoms sufficient to bring patients to the roentgenologist for gastrointestinal examination will lead to the discovery of diaphragmatic hernia in roughly two out of 100 patients.

However, when dealing with the pregnant woman, the incidence of hiatus hernia appears to be much higher than this. Rigler and Eneboe³ examined 195 women during the third trimester of pregnancy. Of 116 multiparas examined, hiatus hernia was demonstrated in 21 (18.1 per cent); in 79 primiparas, 4 were found (5.1 per cent). The combined incidence was 12.8 per cent. Of 10 positive cases re-examined after delivery, the hernia could be redemonstrated in only 3 patients. Great care was taken to distinguish between diaphragmatic hernia and regurgitation into a dilated esophagus. An attempt was made at correlation between gastric symptoms reported by these patients and the presence or absence of a hernia. No such correlation could be determined. On the contrary, there seemed to be a greater tendency to pyrosis and gastric distress in those individuals who showed simple regurgitation into the esophagus.

On the other hand, Diddle and Tidrick⁴ have reported a patient who died during the first stage of her fourth labor from strangulation of the viscera in a diaphragmatic hernia and have found four similar fatal cases in the literature. It is apparent that a diaphragmatic hernia in a pregnant woman must be considered as potentially dangerous, especially when portions of the abdominal viscera other than the stomach are included in the hernia.

It is well known that diaphragmatic hernia can cause symptoms⁵ resembling those caused by peptic ulcer or gall bladder pathology, often somewhat atypical, and often exaggerated upon assuming the recumbent position. Prolonged histories of slight dysphagia or pyrosis,

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unexplained anemias,⁶ or anomalous cardiac symptoms, frequently postprandial and relieved by vomiting but not by food, have been symptom complexes solved in certain instances only by the discovery of an hiatus hernia. This protean nature of the clinical picture led Hedblom⁷ to state: "The etiology of diaphragmatic hernia is often obscure, its pathologic anatomy diversified, and its clinical manifestations manifold."

Even though it is admitted that an appreciable percentage of diaphragmatic hernias may be symptomless, it would seem strange not to find symptoms of such a functional and anatomic defect as this, shown as it is to be unusually common in the pregnant woman. One would expect such symptoms in particular to be precipitated during the stress and strain of labor.

Reports of such complications are not common. A case is recorded⁸ of emesis of blood twice during a twenty-seven-and-one-half-hour labor in a patient without previous gastric symptoms. Labor was terminated by forceps. Occasional heartburn after delivery led to roentgenologic examination of the stomach which revealed one-fourth of this organ above the diaphragm.

DeLee and Gilson⁹ report the partial strangulation of the viscera in a diaphragmatic hernia during the puerperium. This case was apparently not checked by roentgenologic examination.

Evans and Bouslog¹⁰ have recently reported four cases, termed "intractable heartburn of pregnancy," and characterized by severe epigastric distress or burning, appearing after the twentieth week of pregnancy, unrelieved by the usual gastric medication and usually aggravated by the recumbent position. Following delivery, the distress disappeared promptly and the herniation causing it could not be again demonstrated.

In all probability, diaphragmatic herniation of part of the stomach in the pregnant woman is responsible for more epigastric distress and pain than is realized. In retrospect, it is easy to recall an occasional patient who did not respond to the usual gastric remedies and in whom adequate roentgenologic study might have revealed an hiatus hernia. The tendency is to ascribe these symptoms to aberrant function, or to enlargement of the uterus with a resulting mechanical displacement of the abdominal viscera. This view is encouraged by the disappearance of distress post partum.

The possibility that this might be a relatively frequent but often undiscovered symptom correlation justifies the publication of the following case.

Case Report

Mrs. B. McC. (No. 2186), born Aug. 3, 1917, was first seen in the present illness on Nov. 25, 1941. The patient's last menstrual period had occurred Sept. 20, 1941, and she complained of nausea, pain in the back, and headaches. Onset of menses had occurred at approximately twelve years of age and had been somewhat irregular with a duration of five to seven days. A first pregnancy had resulted in miscarriage (said to have been spontaneous) at two months in May, 1938. Curettage was performed for retained placental tissue at Springfield (Illinois) Hospital. A second pregnancy terminated in the spontaneous delivery

of a living male infant after a nineteen-hour labor. Gestation and puerperium were apparently uneventful. The past medical history included measles, mumps, chickenpox, and pertussis as a child. No serious illness had ever occurred. The family history was negative.



Fig. 1.—Film of the case reported, taken in a moderate Trendelenburg position, and revealing a portion of the stomach above the diaphragm and passing through the esophageal hiatus.

Upon physical examination, the weight was 134 pounds and blood pressure 124/70. Urine examination was negative (and subsequently remained so). Head, chest, abdomen, and reflexes were normal. The blood Kahn and Eagle were both negative. The perineum had been markedly lacerated. The cervix was moderately lacerated, ulcerated and nodular. The fundus was softened and slightly enlarged. Adnexa were negative to palpation.

The course of the pregnancy was for the most part uneventful. Life was noticed about Jan. 21, 1942. Blood pressure dropped to 85/50 and remained low. During the first part of March, 1942 (approximately the twenty-third week), a moderately severe but intermittent epigastric pain appeared. Within two weeks the pain had become more constant, bore no constant relationship to food and seemed to be aggravated by lying down. It would awaken her at night and often would be relieved by assuming the erect position. Nausea was infrequent and the relatively few vomiting attacks did not always bring relief. Belching would relieve only at times. Various antacids and gastric sedatives were tried without relief. By May 6, 1942, the uterus was 6 cm. above the umbilicus and the head engaged. The blood pressure was 82/50. The weight had remained at about 143 pounds for several weeks. Roentgenologic examination (Dr. D. M. Sirca) on May 8, 1942, revealed an hiatal hernia (Fig. 1). This film was obtained in the moderate Trendelenburg position. Further fluoroscopic observation identified gastric mucosa above the diaphragm.

During May, 1942, the pain at times was quite severe and the patient was unable to obtain adequate rest at night. Because of the increasing severity of symptoms, induction of labor was advised and the membranes were ruptured artificially at 5:45 P.M. on May 26, 1942, in St. John's Hospital (Springfield, Illinois) about one month ahead of term. Sporadic contractions occurred next day and during the evening of May 27 the patient had an emesis of coffee-groundlike material. Labor began definitely about 2:00 A.M. on May 28. During the ensuing morning, two further emeses occurred, both made up largely of dark brown blood. At 12:30 P.M. on May 28, 1942, a living male child, weight 5 pounds 14 ounces, was delivered spontaneously. The puerperium was marked by the disappearance of all epigastric pain by the fourth day and the patient since has remained symptom free. Strenuous efforts to demonstrate the hiatus hernia roentgenologically three weeks post partum were unsuccessful.

Conclusions

1. Diaphragmatic hernia is being diagnosed with an ever increasing frequency and has been proved to be the cause of a wide variety of symptoms.

2. Under conditions of general practice, symptoms sufficient to bring the patient to the roentgenologist for examination will reveal a diaphragmatic hernia in about two out of 100 patients.

3. It has been pointed out that "intractable heartburn" of pregnancy, appearing after the twentieth week, unrelieved by the usual gastric medication and usually aggravated by the recumbent position, may well constitute a rarely recognized symptom of diaphragmatic hernia.

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ON THE EMPLOYMENT OF OCTOFOLLIN FOR THE RELIEF OF MENOPAUSAL SYMPTOMS, FOR THE SUPPRESSION OF LACTATION, AND IN GONORRHEAL VAGINITIS

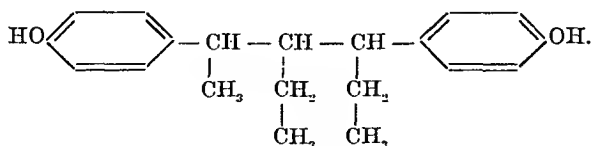
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(*From the Gynecological and Obstetrical Service of the Boston City Hospital*)

ONE of the most important advances in the field of estrogen therapy in recent years was the discovery that synthetic chemical compounds, structurally unrelated to the natural occurring steroid hormones, were sufficiently estrogenic and free from toxicity to warrant their clinical use. These compounds had the advantage of being effective when administered orally. Since 1938, when Dodds, Lawson, and Noble¹ reported the high estrogenic activity of diethylstilbestrol, many reports of its use have appeared in the literature. A recent review by Morrell² and the report of the Council on Pharmacy and Chemistry³ would seem to make an extensive reference to this literature unnecessary here.

Although permanent damage has never been established on the basis of blood, urine and liver function tests, the incidence of untoward side reactions following the administration of diethylstilbestrol cannot be completely ignored.

I wish to report my results with a new synthetic estrogen, not a derivative of stilbestrol, with which I have done extensive clinical work. The compound has the trade name Octofollin,* and is a 2,4-di(para-hydroxyphenyl)-3-ethyl hexane. It has the following chemical configuration.



It might be mentioned here that it is impossible to write this chemical formula in any way to resemble the natural estrogen, as could be done with diethylstilbestrol. Clinical results upon a selected group of menopause patients treated with this substance, then called 118 B, have been reported by Freed, Eisin, and Greenhill.^{4, 5} The chemical researches leading to the development of this estrogen and the physiologic work demonstrating its efficacy and safety have been reported.⁶⁻⁸

*Product of the Research Laboratories of Schieffelin & Co., New York.

Material and Results

Octofollin was employed in this series of cases in tablets of 0.5, 1, 2, 5, and 10 mg. and in suppositories containing 1 mg. each.

The patients have been for the most part from the clinical services of the Boston City Hospital, with the addition of seven menopause cases from the private practice of Dr. John T. Williams. The results on 87 patients are given here, and are grouped according to the condition for which they were receiving treatment.

Menopause.—Fifty-three patients are reported upon and may be divided into two groups, natural and postoperative. Dosage ranged from 1 to 40 mg. daily. Because of this extreme range it is impossible to present these data in tabular form as did Freed. The results can be summarized best in the following manner:

Natural menopause: Of these 37 patients, 24 reported complete relief of symptoms on dosages of 1 to 20 mg. daily. Ten patients reported no relief, or no appreciable relief on 1 to 40 mg. daily. Some of these latter group might have obtained relief on higher dosages. Of these 10 patients, 5 were extremely refractory to any estrogen therapy, receiving no relief from theelin injections (2,000 I.U. 3 times a week) or from stilbestrol in tolerable doses. One of these patients subsequently was relieved by psychiatric therapy. Three patients reported considerable relief on higher dosages and are of course included in the first group of 24.

In but two cases was treatment stopped because of nausea and vomiting, and these patients were both receiving but 1 mg. of Octofollin daily. Short episodes of slight nausea, of doubtful origin in some instances, were reported by ten patients. All of these cases obtained relief on daily dosages, in many instances considerably higher than those at which their nausea had appeared.

Artificial menopause: Of these 16 patients treated with Octofollin, 9 reported complete relief of symptoms, which in 6 cases had been classified as severe, on levels of 2 to 10 mg. daily. Two patients reported considerable relief on 2 to 10 mg. daily, and 5 patients experienced no relief with daily dosages of 2 to 40 mg. daily. One of these 5 patients received no relief from any estrogen therapy and but one, slight relief from theelin injections. Slight nausea was reported by but one patient and therapy was not discontinued in any case because of side reactions.

Unpublished clinical data suggested that the postoperative menopausal symptoms might be harder to control than those arising during the course of the natural climacteric. In this series this did not prove to be the case. The percentage of complete relief was about the same in both groups, and while they are too small for accurate statistical calculation, the dosage level in the artificial menopausal group was the lower.

These results for the entire menopausal group show a higher level of effective dosage than that reported by Freed and his co-workers. It is recognized that this group of patients was smaller and considerably less homogenous than their carefully selected assay group. It is felt also that the average daily dose when calculated for the entire group, about 8 mg. daily, is toward the high side, because of seven patients receiving 20 mg. daily and one receiving 40 mg. daily. If these 8 refractory cases are excluded from the calculation, the average daily dose is 5 mg. daily.

While Octofollin is available in oil for parenteral administration it was not used during this study, and it is entirely possible that some of the patients reporting slight relief, or no relief with very high dosage, might have obtained some response to injection therapy.

Suppression of Lactation.—Twenty post-partum women in whom for various reasons, it was deemed advisable to suppress lactation, were treated with Octofollin. Fifteen milligrams daily (5 mg. t.i.d.) were given for four days beginning by preference on the first post-partum day. Excellent results were obtained in all cases, even those in whom therapy had not begun until milk was present. There were no toxic symptoms.

Gonorrheal Vulvovaginitis.—Fourteen little girls, ranging in age from 8 months to 5 years, were treated orally and topically with this estrogen. In the first series prior to the availability of suppositories, 4 children were treated with Octofollin tablets, 2 mg. daily. In the second group 10 children were treated with suppositories containing 1 mg. of the active estrogen, receiving one suppository three times a day. Excellent and similar results were obtained in both groups. Smears became negative for gonococci by the end of one week of treatment, and vaginal discharge and itching disappeared by the end of the third or fourth week. Slight mammary enlargement, which regressed following cessation of therapy, was noted in two cases, both on suppositories.

Discussion

Two aspects of these data may warrant mention.

First: The cases in the menopausal series were not selected with the idea of assaying Octofollin. As a matter of fact several extremely refractory patients who had shown little, if any, relief with other estrogens, theelin, estradiol benzoate, and stilbestrol were deliberately included. Several of these women, in whom control of symptoms could not be established with stilbestrol because of the onset of nausea and vomiting, were controlled by the use of Octofollin without the gastrointestinal reactions. This would seem to give specific support to the impression that, at the effective levels, Octofollin is considerably less toxic than diethylstilbestrol, and dosage can, therefore, be pushed up to levels where satisfactory symptomatic control is obtained.

Second: It was noted that once relief of symptoms had been obtained the dosage could be decreased in the majority of cases to levels one-fourth to one-half that at which the symptoms had disappeared.

The above considerations, as previously mentioned, make it difficult to state an "average daily dose" which will control the menopause. The effective therapeutic dose varies with the patient and must be individually controlled.

It might be mentioned further that these results bear out the general impression that the menopause clinic groups, particularly in the large charitable institutions, seem less favorable test groups than the more intelligent and reliable private patients. In 6 of the 7 private patients in this study in whom satisfactory results were obtained, the dose was 1 to 3 mg. daily.

Summary

The synthetic estrogen, Octofollin, which is unrelated to stilbestrol, has been given extensive clinical trial in 87 patients suffering from the various conditions for which estrogens are regularly indicated. Excellent results were obtained.

This compound is an effective estrogen and at the clinically effective levels seems to be less toxic than diethylstilbestrol.

I wish to acknowledge my thanks and appreciation to Dr. John T. Williams, Surgeon in Chief, Gynecological and Obstetrical Service, Boston City Hospital, for his help and cooperation in the writing of this paper.

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EARLY PSEUDOMYXOMA PERITONEI IN A CASE OF FETAL MECONIUM PERITONITIS*

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THE following case is pathologically rare, and an even rarer cause of dystocia.

The mother, a 29-year-old white woman, gave no history of past illnesses. She had had two previous normal pregnancies. The present pregnancy was uneventful until the seventh month, when the patient developed edema of the ankles and vulva and frequent headaches. About the beginning of the eighth month the patient also complained for some days of severe pain in the right lower quadrant radiating to the back. The urine tests showed only occasional faint traces of albumin. There was a moderate anemia with 3,400,000 red blood cells and 67 per cent hemoglobin (10 Gm.). Blood pressure was normal. Wassermann was negative. Delivery was due Aug. 17, 1941. On August 2 the patient was seen at the prenatal clinic complaining of diarrhea, abdominal cramps, and general discomfort. At this time the abdomen was found rounded and huge, the head floating (R.O.P.), fetal movements present, and fetal heart normal. Cervix admitted one finger. A tentative diagnosis of polyhydramnios was made.

On August 9 at 10 P.M. there was an onset of laborlike but non-continuous pains. The following day at 6 A.M. partial rupture of the membranes occurred. Regular labor pains started two days later, on

*Presented at a meeting of the Philadelphia Obstetrical Society, January 7, 1942.



Fig. 1.—Section above perforation. Note (a) irregular and cystic glands, (b) irregular and thin muscular coats, and (c) adhesions.

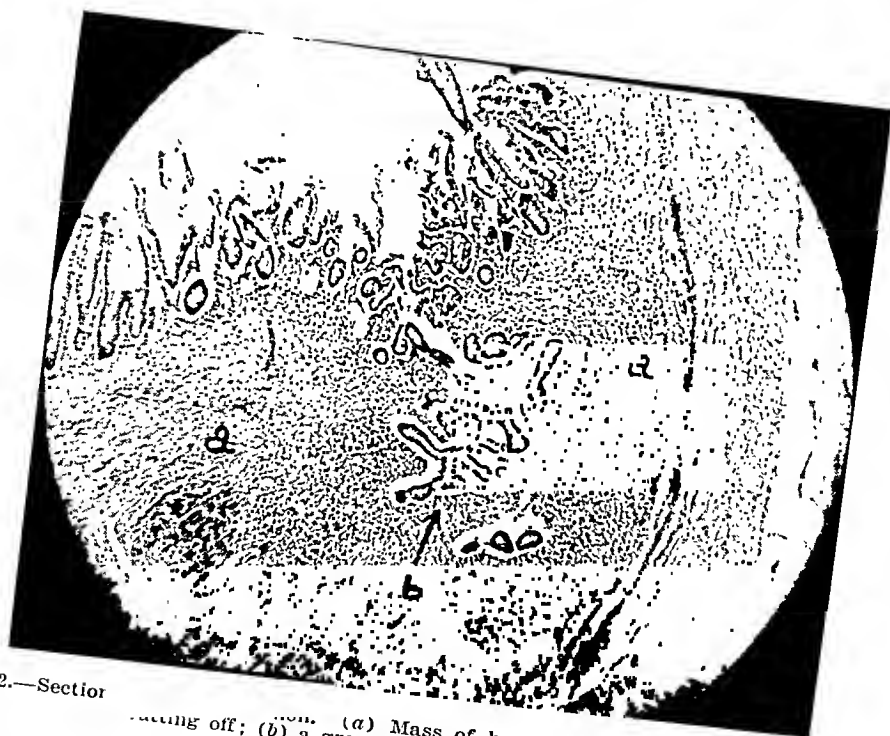


Fig. 2.—Section showing off; (a) Mass of hyperplastic lymphoid tissue partly cutting off; (b) a group of abnormally deep glands.

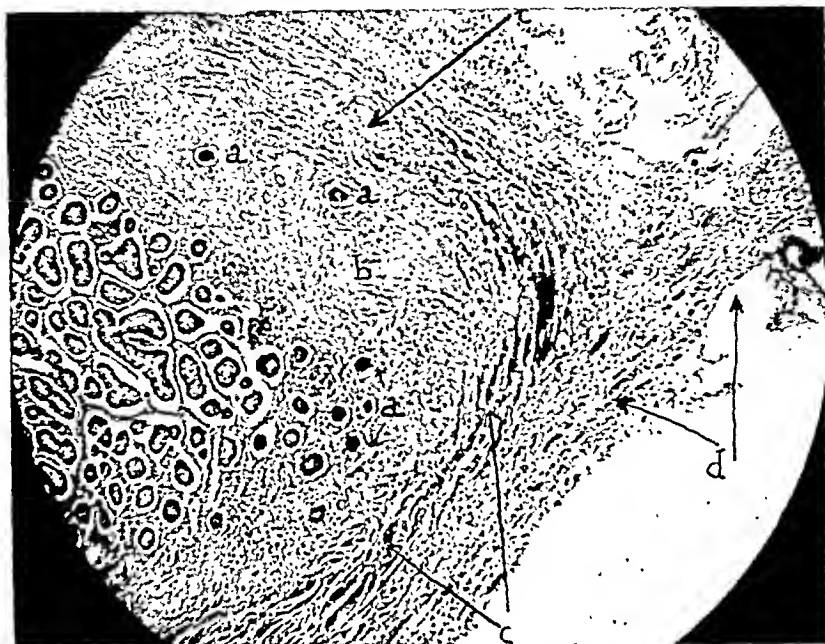


Fig. 3.—Section near perforation. (a) Intestinal glands penetrating in (b) submucosa showing fibrosis, (c) numerous gaps in muscular coats, and (d) adhesions.

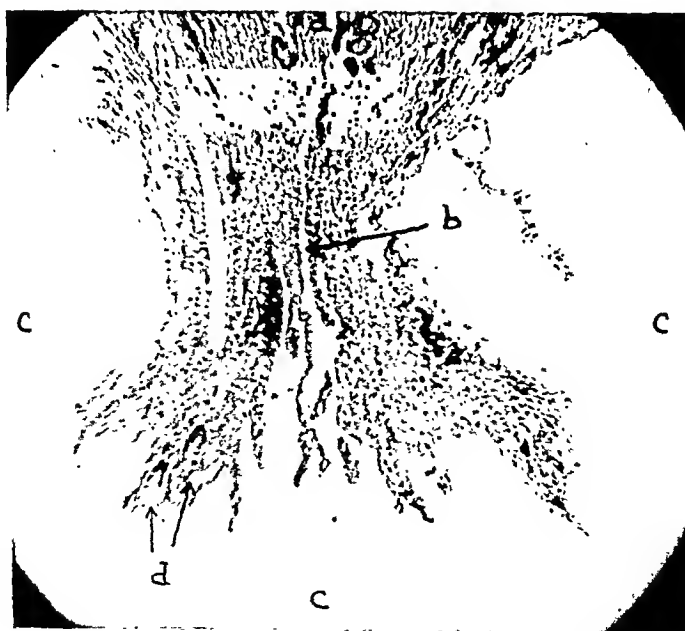


Fig. 4.—Perforation. (a) Lumen, (b) perforation, (c) peritoneal cavity. Note (d) intestinal glands opening in the peritoneal cavity.

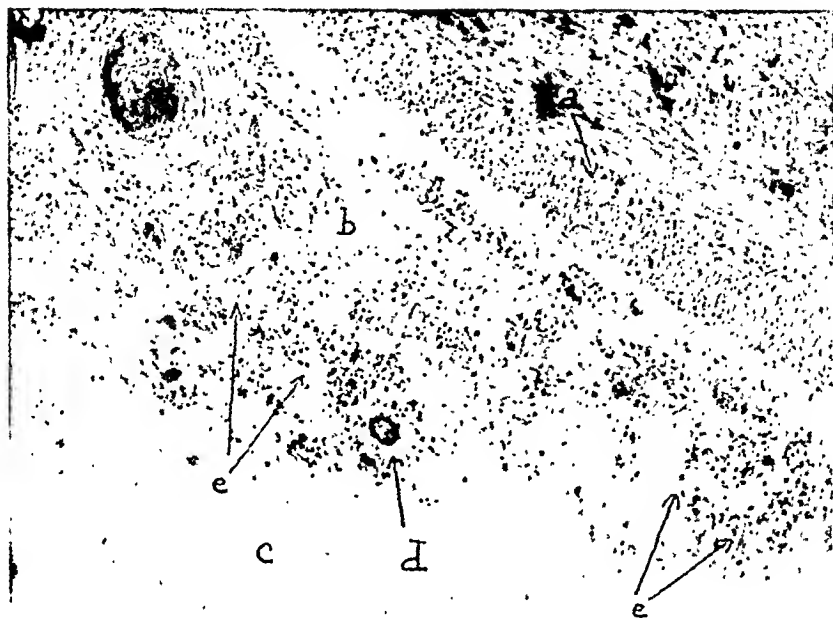


Fig. 5.—(a) Muscular coats of intestinal wall, (b) adhesions, (c) peritoneal cavity. Note (d) a well-preserved intestinal gland implanted on the serosal surface, (e) inflammatory cells and pigment-carrying histiocytes.



Fig. 6.—Pseudomucinous mass. Note trabeculae of fibrous tissue, stellate cells separated by mucoid material, calcified masses (lower right).

August 12 at 3 A.M. At 11:55 A.M. the head was engaged and at 12:55 the second stage was terminated by Simpson low forceps. The head was delivered with moderate difficulty, but great difficulty was encountered in delivery of the shoulders and of the abdomen which was greatly distended. The baby, a male, was deeply cyanotic. The breathing was limited to a few gasps; the heart beat ceased shortly after delivery.

Following delivery of the child about one gallon of amniotic fluid poured out.

Autopsy showed the body of an apparently full-term baby, weighing 3,980 Gm., and presenting extreme cyanosis. The abdomen, greatly distended, was 40 cm. in circumference at the navel. Fluctuation was very evident. No other abnormalities were found on external examination. The thoracic organs showed extreme congestion.

Abdomen.—The different layers of the anterior abdominal wall were edematous and congested and showed numerous small hemorrhages. The abdominal cavity contained about 300 c.c. of slightly cloudy straw-colored fluid. The greater part of the small intestine was matted together by organized adhesions which fixed it in the right iliac fossa. The ascending and transverse colon were also partly covered by adhesions, while the omentum was retracted and rolled up.

Careful separation of the adherent intestinal loops showed a greenish jellylike mass with white opaque areas about 2 by 1.5 cm. firmly adherent to the outer wall of the terminal ileum, opposite the mesentery, about 10 cm. from the ileocecal valve. The serosa covering most of the small intestine and part of the colon was thickened and opaque. Stomach, liver, and spleen were free from adhesions. The lumen of the small intestine was patent throughout, but narrower below the point to which the mucoid mass was attached. At this point the mucosa presented an infundibular depression. No gross perforation was found.

All other organs showed extreme congestion and small hemorrhagic foci. The cause of death was ascribed to asphyxia during prolonged labor.

Serial microscopic sections of the segment of small intestine to which the mucoid mass was attached revealed numerous abnormalities: several glands of the mucosa were dilated and cystic. In other places there were hyperplastic masses of lymphoid tissue, apparently cutting off groups of intestinal glands. The submucosa showed marked fibrosis and contained inflammatory cells. In one place numerous glands were scattered deep in the submucosa and surrounded by fibrous tissue. The muscular coats were very irregular in their structure and presented numerous gaps. At a point near where there were groups of abnormally deep glands, a perforation was found. The intestinal mucosa was redundant in this area and seemed to have herniated through the gap in the wall. At the site of the perforation, the intestinal wall consisted mostly of fibrous tissue infiltrated with mononuclear cells. Some isolated well-preserved tubular glands could be seen in the surrounding fibrous adhesions, together with inflammatory cells, pigment-carrying histiocytes and small calcified masses. The mucoid mass described grossly showed thin trabeculae of fibrous tissue between which were a number of stellate connective tissue cells separated by abundant intercellular substance which gave the reaction of mucin. There also were mononuclear inflammatory cells, histiocytes loaded with yellow-brown pigment, and masses of calcified material.

This is a case of the so-called fetal meconium peritonitis, that is, a "chemical and foreign body peritonitis occurring during intrauterine

life as the result of abnormal communication between the bowel contents and the peritoneal cavity" (Boikan). In this case the presence in the peritoneal cavity of living and secreting intestinal glands accounts for the presence of the mucoid mass. The condition is comparable to pseudomyxoma peritonei following rupture of a mucocele of the appendix.

I believe that in this case the underlying cause was a developmental abnormality consisting of abnormally deep groups of intestinal glands and of a congenital weakness of the muscular coats. Some of the deeply situated glands being partly cut off from the mucosal surface may gradually have become cystic and finally ruptured into the peritoneal cavity through one of the gaps in the muscular coats. This would account for the perforation of the gut and the spilling of meconium into the peritoneal cavity.

EXTENSIVE HYDATIDIFORM MOLE FORMATION WITH LIVING CHILD

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CASES of twin pregnancies have been reported in which one ovum developed normally while the other formed a hydatid mole. We are concerned here, however, with the disturbance of a single ovum. Novak¹ believes that the hydatidiform mole is a neoplasm rather than a structure resulting from degenerative changes. Since chorionepithelioma, a truly malignant neoplasm, follows from 2 to 10 per cent of hydatidiform moles, this view seems logical.

Greenhill² has stated that a fetus is seldom found where a hydatidiform mole is present. This seems to be the view generally held. In 9,501 deliveries at the Queen's Hospital, Honolulu, from 1932 to 1941 inclusive, there was only one recorded instance of a single ovum with coexisting fetus and hydatidiform mole. This was in a multigravid Filipina of 27 years who delivered large masses of grapelike material and a macerated fetus of four and one-half months. Histologic examination revealed the typical picture of hydatidiform mole. Williams³ reported in 1918 that no instance of viable fetus had been found together with hydatidiform mole formation of the placenta in 17,930 obstetric cases treated in the Johns Hopkins Medical School. Meyer⁴ has made a careful study of a large series of hydatidiform moles in the Carnegie Institute of Embryology, which suggests that the occurrence of an embryo in a mole is not very rare. In this large collection of hydatidiform moles, 64.4 per cent contained fetuses in an excellent state of preservation and of an average age of 66.6 days.⁵ In an otherwise normal pregnancy and delivery with a living child, it is not unusual to note small areas of mole formation. Several reliable writers (Hertzer,⁶ Frank,⁷ Playfair,⁸ Adami⁹) have attested to this. Hirst¹⁰ remarks that if the disease does not begin until after the villi of the chorion have atrophied, or if the degeneration is confined to a comparatively limited area, the pregnancy usually proceeds to term or to the point of nonviability of the fetus. Titus,¹¹ Greenhill² and DeLee¹² confirm this statement.

A careful search of the medical literature available here in Hawaii yields an account of only one fairly authentic case of hydatid mole formation of the placenta accompanied by the birth of a living child.⁵ This specimen filled a two-liter jar and was said to have accompanied a living seven months' fetus which was expelled between the time of passage of the fetus and the placenta. Unfortunately the placenta was not saved. No notes are appended as to how long the fetus survived. No doubt there have been other, unreported, cases similar to the aforementioned one.

A case recently came under our care and we have been sufficiently impressed by its rarity to feel justified in the following review.

Case Report

Mrs. G. J., aged 18 years, was admitted to the Kapiolani Maternity Hospital on Sept. 23, 1942, not in labor, at seven and one-half months of her second pregnancy. The pregnancy had been uneventful until two weeks previously at which time moderate albuminuria and beginning pitting edema of both ankles was noted. There were no headaches nor vertigo and blood pressure was 114/78. A salt poor, high protein diet was advised. In addition, ammonium chloride, grains 15, was given thrice daily. Albuminuria and pitting edema progressed however, and in addition hematuria set in and hyaline and granular casts began to appear in the urine. There was also a weight gain of eight pounds in nine days. Despite a normal blood pressure there were no headaches or dizzy spells. Other laboratory data were as follows: Red cell count 4.19 million, hemoglobin 78 per cent. Blood clotting time was six minutes; blood type was A. Blood Wassermann and Kahn were negative. Unfortunately no blood serum protein determinations were made. In view of the subsequent findings in this case, it should be noted that there was no vaginal bleeding before the time of her delivery.

This patient had been delivered one year previously, at the age of 17, of a stillborn macerated fetus at seven months. The labor had begun spontaneously and was preceded by high blood pressure, albuminuria, and generalized edema. The age of the fetus was estimated at about 6½ months. The placenta was noted at the time by the physician who delivered her to have been "dull gray and fibrotic on three quarters of its surface." No histologic study of the placenta was made and the blood Wassermann was not done at that time. Convalescence was uneventful. There were no other noteworthy points in her past history nor in the family history.

With her present admission (her second pregnancy), generalized edema was noted, with marked pitting of her lower legs and feet. The blood pressure was 120/70 and the urine showed 3+ albumin, 1+ red blood cells, and no casts. Fetal heart tones were of good quality, 160 per minute, and loudest one inch below and to the left of the umbilicus. After three days of rest and ammonium chloride therapy, with high protein and salt poor diet, it was felt advisable to induce labor, bearing in mind the loss of her first baby in the seventh month under similar circumstances. Uterine contractions were induced readily by the administration of castor oil, an enema, and repeated small intramuscular injections of pituitrin. Vitamin K was given intramuscularly at the onset of labor. After four and one-half hours of uneventful labor, during which time no sedatives of any kind were given, a well-developed though small

female infant was born normally and cried at once. Almost immediately two translucent vesicles slightly larger than peas emerged from the vagina. The cord was clamped as soon as it ceased pulsating. Palpation of the uterus revealed a cylindrical enlargement occupying its entire right side. The presence of a twin was suspected. Confusion was added by the occurrence of a furious hemorrhage, total blood loss being estimated at 1,500 c.c. The patient received 1,000 c.c. of 5 per cent glucose solution at once and 500 c.c. of whole blood soon after. In the meantime the operator removed several huge masses of grapelike vesicles from within the uterus. The severed umbilical cord emerged from typical hydatid mole tissue and there was virtually nothing present in this mass which grossly resembled placental tissue. The amount of molar tissue together with the umbilical cord removed at this time weighed 4 pounds 2 ounces and the live child weighed 4 pounds 6 ounces. By now the uterus was down to a size consistent with that of a normal puerperal organ and bleeding had nearly stopped. It was considered unsafe to proceed with any further exploration of the uterine interior although it was suspected that more molar tissue might be present. During the following three days, three large masses of tissue, not in the least resembling normal placenta, were passed. These masses were composed of material looking like bunches of machinists' cotton waste. If there had been vesicles in it, these had disintegrated and were unrecognizable as such. These fragments weighed a total of 4 ounces, which, added to the original 4 pounds 2 ounces, made a total weight of 4 pounds 6 ounces, the same weight as that of the baby.

Convalescence was uneventful except for a slight fever. The patient left the hospital on the seventh post-partum day in good condition. Repeated Friedman tests were consistently negative, as were the urinalyses. The baby developed a series of troublesome subcutaneous abscesses in various parts of the body and had a stubborn diarrhea. These setbacks were gradually overcome, and when last seen, eight months after delivery, the infant was gaining rapidly and seemed quite robust and normal.

Pathologic Report

The gross specimens were examined by Dr. I. L. Tilden who reported as follows: The placenta together with the umbilical cord weighed 4 pounds 6 ounces (2,100 Gm.). It measured 25 cm. in diameter and 6 to 10 cm. in thickness. The umbilical cord was attached eccentrically and measured 30 cm. in length and 2 cm. in diameter. The umbilical vessels on the fetal surface of the placenta were dilated and tortuous, varying in diameter from 5 to 20 mm.; they were filled with recent blood clot. One amnion and one chorion were present.

The placenta was made up of alternating masses of cystic bodies and coarse, friable, stringy, noncystic tissue. The individual cysts were generally large, some measuring 3 cm. in diameter. The intervening tissue was edematous and extremely coarse and friable. Several hemorrhagic areas were present which were even more friable. It was estimated that approximately one-half of the placenta had undergone cystic degeneration.

Microscopic examination of the cystic tissue revealed the changes associated with hydatidiform mole with, however, certain minor variations. Many of the giant villi had undergone cystic changes only in their central portions, leaving relatively thick walls (Fig. 2). The villous

stroma making up the larger portion of the cyst walls was edematous and exhibited many areas of beginning cyst formation. Most of the cysts were covered by a single layer of poorly preserved syncytial cells. Generally there was only a slight tendency toward proliferation of the trophoblastic cells although certain fields were present which did show proliferation of both syncytial and Langhans cells (Fig. 3). In certain instances the vascular supply was intact, the vessels having been pushed far toward the periphery by the central cyst formation; in most instances no vascular supply was intact, the vessels having been pushed far to-



Fig. 1.—The gross appearance of the placenta after formalin fixation.

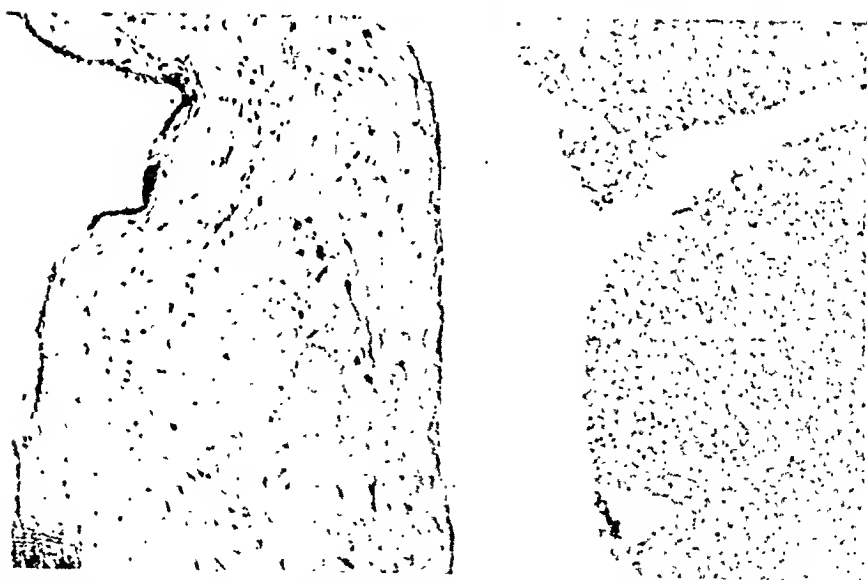


Fig. 2.—Giant villus showing relatively thick wall and central cystic change. Hematoxylin and eosin. (X130.)

ward the periphery by the central cyst formation; in most instances no vascular supply was evident.

The solid friable tissue presented a comparatively normal histologic picture. There was considerable red cell extravasation into the villous stroma but the vessels were intact and the villi were average in size and exhibited no evidence of trophoblastic proliferation.

Extensive necrosis was observed in the sections taken through the hemorrhagic tissue noted in the gross examination. This was characterized by marked red cell extravasation and leucocytic infiltration into the involved villi; actual loss of structure was observed in several areas.

The umbilical cord exhibited a normal microscopic picture.

No evidence of organization was observed in sections taken through the dilated umbilical vessels on the fetal surface of the placenta.

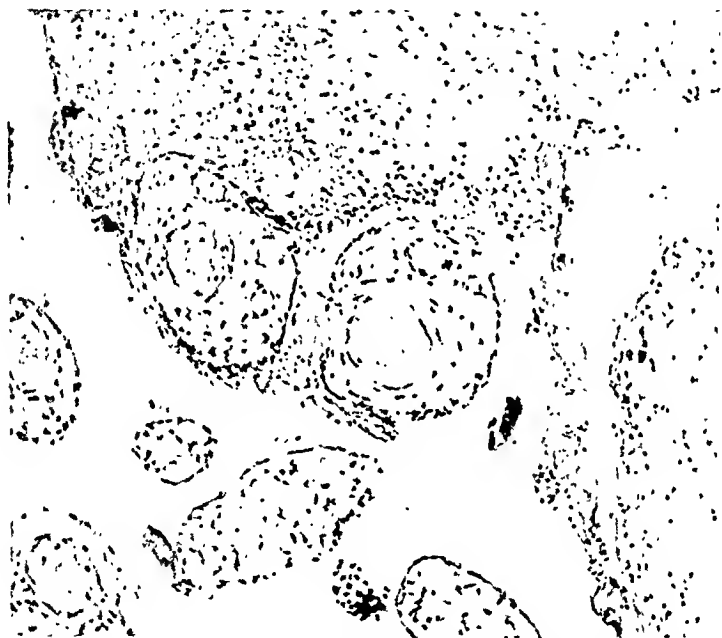


Fig. 3.—Showing necrosis characterized by leucocytic infiltration and red cell extravasation into the involved villi. Hematoxylin and eosin. ($\times 130$.)

Summary

1. The occurrence of a viable baby together in a single ovum with extensive hydatidiform mole formation is exceedingly rare.

2. The subject is reviewed herewith and such a case presented.

3. The mother in this case recovered following normal vaginal delivery, and the infant continued its normal development after a stormy beginning. Subsequent Friedman tests on the mother were negative.

4. The vesicles obtained showed the typical pathologic changes characterizing hydatidiform mole, i.e.: (1) trophoblastic proliferation, (2) hydropic degeneration of the villous stroma, and (3) scantiness of blood vessels.

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Lemmon, Wm. T., and Paschal, George W., Jr.: *Continuous-Serial, Fractional, Controllable, Intermittent—Spinal Anesthesia*, *Surg., Gynec. & Obst.* 74: 948, 1942.

The authors present a statistical report of 1,000 patients operated upon under continuous spinal anesthesia. The point is stressed that this method is safer than the single dose technique for the following reasons:

1. Small dosage.
2. Less absorption of the anesthetic into the circulation.
3. Controllability, by withdrawal of spinal fluid. Of the one thousand cases presented, 30 were operations above the diaphragm, and in only one of these, a lobectomy, was it necessary to use supplemental inhalation anesthesia. There was little difficulty with excessive fall of blood pressure. The percentage of headaches was 2.8, which is approximately what one would expect with the single dose method. There were 34 instances of pulmonary complications. The mortality was 4.7 per cent. In no case was the anesthesia a contributing factor. The operations performed are all tabulated and represent an adequate distribution of cases. Of interest is the fact that 62 cesarean sections and 192 gynecologic operations were carried out with this technique.

L. M. HELLMANN.

Department of Statistics

STUDIES OF SURGICAL MORBIDITY*

I. Abdominal Hysterectomy

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THIS is a study of surgical morbidity based on 800 abdominal hysterectomies. The inadequacies of present morbidity standards are generally recognized and the need for proper interpretation of these variations is apparent. This study includes the incidence, the factors, and the etiology of morbidity.

The 800 abdominal hysterectomies were performed in this institution between January, 1938, and July, 1942. There were 420 subtotal hysterectomies and 380 total hysterectomies. The study was made in the belief that every clinic should examine and publish its statistics from time to time for the purpose of discussion and interpretation of the facts found. By doing this, one can eliminate the prejudices, mannerisms, and false impressions which invariably develop over a period of years.

Methods and Material

The series includes both private and service, colored and white patients, operated upon by the seven attending gynecologists and residents. All of the operators used essentially the same technique, and the indications for surgery were quite uniform. Operations by the resident staff were done under the direct supervision of one of the attending gynecologists. This series of patients was studied in the same chronologic order in which the patients were operated upon, and all the abdominal hysterectomies done on the gynecologic service during this period were included.

The operations were graded as to the difficulty of procedure on the basis of 1 to 4, with a Grade 1 being the simplest procedure and a Grade 4 the most difficult type. All grading was done by one individual. The direct pathology, the associated pathology, the operating time, and all of the findings were taken into consideration in the grading of each operation.

General Morbidity

The standard used was as follows: a temperature of 100.4° F. (oral) on any two days postoperatively, excluding the first twenty-four hours, was considered morbid. This very strict standard, derived from the

*Presented at a meeting of the Chicago Gynecological Society, January 15, 1943.

obstetric morbidity standard, was used in order to classify all doubtful and borderline morbidities which are essential to a study of this kind. We well realize that this is not the ideal standard for judging morbidity as is evidenced by our findings of the causes.

Table I shows the morbidity of the entire group, and the morbidity of each of the grades in both types of operative procedure. The morbidity of the entire group was 33.87 per cent, with a morbidity of 36.57 per cent for the total hysterectomy, and 31.42 per cent for the subtotal procedure. Total hysterectomies show a slightly higher morbidity than the subtotal hysterectomies. The different grades show, as would be expected, an increase in morbidity accompanying the more difficult procedures. The Grade 4's in both groups show a morbidity of well over 60 per cent, while the Grade 1's show a morbidity below 30 per cent. With the increased trauma of the more difficult procedure, plus the more extensive pathologic involvement responsible for the Grade 4 operation, one would expect a higher morbidity.

TABLE I. RELATION OF MORBIDITY TO GRADE OF OPERATION

	NUMBER	NUMBER MORBID	PERCENTAGE MORBID
Total hysterectomy	380	139	36.57
Subtotal hysterectomy	420	132	31.42
	800	271	33.87
<i>Total Hysterectomy</i>			
GRADE	NUMBER	NUMBER MORBID	PERCENTAGE MORBID
1	142	40	28.87
2	150	52	41.40
3	61	30	49.18
4	27	17	62.92
	380	139	36.57
<i>Subtotal Hysterectomy</i>			
1	111	27	24.32
2	174	49	28.21
3	91	29	31.86
4	44	27	61.36
	420	132	31.42

TABLE II

	NUMBER	NUMBER MORBID	PERCENTAGE MORBID
Private patients	523	147	28.10
Service patients	277	124	44.78
White patients	573	162	28.27
Colored patients	227	109	48.01

TABLE III. ONSET AND DURATION OF MORBIDITY

DAY MORBIDITY BEGAN	PERCENTAGE	NUMBER OF DAYS MORBID	PERCENTAGE
First	24.1	1	0.7
Second	48.2	2	27.9
Third	5.0	3	22.4
Fourth	5.0	4	13.3
Fifth	4.6	5	12.5

TABLE IV. MORBIDITY CAUSES

CAUSE	GRADE 1	GRADE 2	GRADE 3	GRADE 4	TOTAL	PER-CENTAGE
Unknown	27	48	23	12	109	40.2
Cystitis	16	22	12	7	57	21.0
Pyelitis	3	2	4	3	12	4.4
Thrombophlebitis	2	5	1	5	13	4.7
Pulmonary embolism	5	5	1	0	11	4.0
Wound infection	5	3	2	3	13	4.7
Local infection	1	4	6	2	13	4.7
Anemia	0	2	1	1	4	4.0
Upper respiratory infection	4	4	2	1	11	2.9
Paralytic ileus	1	2	2	3	8	1.4
Dehydration and shock	1	0	0	2	3	1.1
Vaginal hemorrhage	0	1	1	0	2	0.7
Injured ureter	0	0	0	2	2	0.7
Abscess (breast, axillary, peri-anal)	1	1	1	0	3	1.1
Peritonitis	0	1	0	1	2	0.7

Table II shows the number of private and service patients with the corresponding morbidity for each, as well as the number of colored and white patients and their morbidity.

Table III shows the relation of morbidity to the number of days the patients were morbid, and the days on which they became morbid. Seventy-two per cent of the patients became morbid on the first 2 post-operative days, and 86 per cent became morbid within the first five days. Fifty per cent of the morbid patients were morbid for two or three days, and another 25 per cent were morbid for only five days.

Morbidity Causes

Table IV shows the causes of morbidity of both the total and subtotal groups in their respective grades. In order to call any one factor the cause of the morbid condition, it had to be shown by substantial confirmatory evidence to be the etiologic factor. The laboratory findings, the time of onset of the morbid condition, and the clinical picture were all taken into consideration in establishing the cause of the morbid condition, in this case the cause of the rise in temperature.

Any patient who was morbid according to the standard used, but for whom there could not be found a substantiating cause, was classified as "unknown." They were, for the most part, those patients who had a temperature above 100.4° F. for the first few days after surgery. The temperature sometimes rose as high as 102° F. and then gradually returned to normal in the next two or three days. These patients made an uneventful recovery and did not remain in the hospital any longer than the nonmorbid patients. There were patients who unquestionably had a definite pathologic etiology for their morbidity which was not detected.

Cystitis was diagnosed on the basis of daily urinalysis in the presence of both clinical symptoms and the temperature rise which characteristically appeared on the fourth or fifth postoperative day. Table IV shows that 25 per cent of all morbidities were due to either cystitis or pyelitis. When the "unknown" group is subtracted from the series, the urinary infections are found to be the etiologic factor in 43 per cent of the morbid patients. It was also noted that there were 64 patients in whom the urine was apparently "infected," but there was no rise

in temperature. The "nonmorbid" urinary infections occurred in 8 per cent of the patients with an incidence of 6.8 per cent for the total hysterectomies, and 9 per cent for the subtotal hysterectomies. Catheterized urine specimens to be called "infected" had to show more than 20 mg. of albumin and more than 10 white blood cells per high power field on two consecutive days postoperatively.

"Local infection" was an infection of the operative field, usually at the site of the cervical stump. There were 13 patients with this type of infection.

"Wound infections" were those infections of the incision which were responsible for temperature rises above the standard. That there were the same number (13) of these as there were local infections is coincidental.

There were 11 upper respiratory infections and all so classified were minor in nature.

Of the 11 patients with pulmonary embolism in the series, 10 occurred in the first two grades, i.e., the easier operative procedures. Five of these embolisms proved fatal. Eight of the 11 were in colored patients. Four embolisms occurred in the total operation, while seven occurred in the subtotal procedure. Only two of these patients with embolism had a diagnosed thrombophlebitis and both of these involved the leg. There were 13 patients with thrombophlebitis diagnosed as the etiologic cause of a morbidity.

An axillary abscess and a breast abscess followed the injection of subcutaneous fluids given in that area.

There were two patients in the series with evisceration, but only one of them became "morbid."

There were two instances in which the ureter was injured. One was in a subtotal operation and the other in a total hysterectomy, and both were Grade 4 operative procedures.

There were 3 patients in whom injury to the bowel was a morbidity factor.

Relation of Pathology to Morbidity

Table V (a and b) shows the relation of pathology to morbidity. Each operation was classified as to its predominate pathologic condition.

Under the heading "undetermined pathology" were included patients with functional bleeding, endocrine dyscrasias without demonstrable pathology, lacerations of the childbirth canal without any other pathologic condition, and patients with a pregnancy where a hysterectomy was done therapeutically and the cause for the operation was not demonstrable pathologically. It is also worth while to point out that in the group of patients classified under "undetermined pathology," the morbidity rate is very near that of the general overall morbidity average.

Classified under "tumors" were patients with benign neoplasms of either the uterus or adnexa. These operations were not complicated by any other pathologic conditions, such as adhesions from "residues," endometriosis, or previous surgery.

Classified under "previous operations" were patients who had associated pathology, usually adhesions resulting from previous abdominal surgery, but who did not have either "residues" of pelvic infection or endometriosis. Most of this group were patients with fibroids, adhesions and a history of previous surgery. Adhesions resultant from previous surgery did not increase the morbidity over the general average.

TABLE V. RELATION OF PATHOLOGY TO MORBIDITY

	GRADE 1 % MORBID	GRADE 2 % MORBID	GRADE 3 % MORBID	GRADE 4 % MORBID	AVERAGE PERCENTAGE MORBIDITY
<i>Total Hysterectomy (a)</i>					
Tumors	22.2	30.7	20.0	100	26.7
Residues	66.6	42.5	60.7	58.3	51.6
Endometriosis	35.2	24.3	50.0	66.6	33.8
Undetermined	36.8	--	--	--	36.8
Malignancy	15.3	70.0	100	100	51.7
Previous operation	33.3	26.6	30.0	33.3	29.4
<i>Subtotal Hysterectomy (b)</i>					
Tumors	23.6	32.7	39.2	66.6	25.5
Residues	25.0	32.3	37.6	59.0	36.0
Endometriosis	17.6	27.7	37.5	63.6	33.8
Undetermined	33.3	25.0	--	--	31.2
Malignancy	50.0	--	--	50.0	25.0
Previous operation	--	33.7	20.0	66.6	33.3

Under "endometriosis" were included all patients who had any endometriosis without associated malignancy, or "residues" of pelvic infection. If a patient had both a benign tumor and endometriosis, she was classified under endometriosis.

Under "residues" were included all patients who had the residues of previous pelvic inflammatory disease, either specific or nonspecific in nature. All adhesions in the pelvis, not explained by previous surgery or endometriosis, were considered to be evidence of some inflammatory process having been present. The term "residues" is one used in this series to denote the pathologic entities resulting, or residual from any previous pelvic infection, regardless of the etiology. Differentiation between specific and nonspecific types of "residues" was not made in this study. Patients with "residues" of pelvic infections had a high percentage of morbidity. In the total group it was 51 per cent.

Patients with any type of malignancy were classified under that heading, taking precedence over all other types of pathology. In the "malignant" group there were 5 patients with chorionepithelioma, and 4 patients with sarcoma of the uterus. There were 19 patients with carcinoma of the endometrium, which constituted over 50 per cent of the malignancies. There were 3 patients with carcinoma of the cervix, and 2 of these were found incidentally by the pathologist after the uterus had been removed for other causes. There were 6 patients who had carcinoma of the ovaries. In the total hysterectomy group, the malignancies show a very high morbidity rate. There were three and one-half times as many patients with malignancies operated upon in the total hysterectomy group as in the subtotal group. In Grades 3 and 4 of the total group, the morbidity is 100 per cent, and in Grade 2 it is 70 per cent.

In this series there were 32 patients who had the appendix removed. These appendices were removed either because they showed evidence of previous disease, obstruction to drainage, or there was a history of recurrent attacks. Eleven of these patients were "morbid" (34 per cent).

Mortality

There were 10 deaths in the series, giving a mortality rate of 1.25 per cent. Table VI shows the distribution of deaths in the grades and the causes. They were divided into 6 deaths in the subtotal group, and 4 deaths in the total hysterectomy group. This gives total hysterectomy a mortality rate of 1.05 per cent, and subtotal hysterectomy a mortality rate of 1.43 per cent.

TABLE VI. MORTALITY

10 Deaths, 1.25%		5 deaths pulmonary embolism, 50%
		5 deaths other causes, 50%
Total hysterectomy, 4 deaths, 1.05%		Subtotal hysterectomy, 6 deaths, 1.43%
Grade 1, 1 (peritonitis and pneumonia)		Grade 1, 1 (pulmonary embolism)
Grade 2, 1 (peritonitis and paralytic ileus)		Grade 2, 4 (3 pulmonary embolism; 1 anesthetic)
Grade 3, 1 (pulmonary embolism)		Grade 3, 0
Grade 4, 1 (peritonitis and pneumonia)		Grade 4, 1 (uremia)

Discussion

The word "morbidity" is defined by Webster's dictionary as "(1) being in a diseased or abnormal state; (2) caused by or denoting a diseased condition; (3) of or pertaining to disease; pathological." The word is derived from the Latin "morbidus" meaning "affected with or pertaining to disease." The connotation of the word when used in a study such as this has to do with those deviations from the ever elusive term "normal postoperative course."

The need for a standard of morbidity in surgical procedures is of utmost importance. The need is not to set up a standard by which individual patients can be judged morbid or nonmorbid, but rather to set up a standard by which groups of patients in studies such as this can be evaluated and compared to other such studies. There is no universally accepted standard today by which such a study can be made. The numerous and various standards in use today have, for the most part, emanated from the obstetric standard, similar to the one used in this study. Because of years of attacks on the maternal and fetal morbidities and mortalities, the obstetrician has established and agreed upon a standard. However, the surgeon's work is so varied, and there are so many factors entering into the establishment of an effective, workable standard that it has not been feasible. Emergency, traumatic, and elective surgery, as they vary in each of the surgical specialties, all contribute to the confusion. It has been suggested that a standard should be worked out for each of the more common surgical procedures; i.e., appendectomies, herniorrhaphies, mastectomies, cholecystectomies, hysterectomies, etc. The importance of such a standard is not to set up an axiomatic law under which all morbid patients will fall into "pigeonholes" of classification, but to act as an average, or "norm," for the purpose of analysis and comparison.

It is not possible for one group to establish a standard from one study such as this. The representatives of various organizations examining numerous series of patients, and studying the results of a composite group in an analytical manner, could alone set up such a standard which would be both workable and acceptable. With such a morbidity standard our efforts could then be directed toward those factors which are now responsible for the complications arising from surgery.

It has not been our purpose in this presentation to advocate either the subtotal or the total hysterectomy as a routine operative procedure. We cannot emphasize too strongly our objection to "routine" surgical operations in gynecology. Adherence to fundamental surgical and pathologic principles results in rational variation to individual problems. The experience of the operator, the pathology involved, and the difficulty of the individual operation are extremely important in judging which operation is the procedure of choice.

The grading of the individual operations was considered a most fundamental part of the study, for it is only by comparing similar types of operations in relation to their pathology and operability that a fair comparison can be made. It has been brought out (Table I) that morbidity rises with increased technical difficulty rather than being associated with either operative procedure per se.

In evaluating the literature on mortality and morbidity in hysterectomies, it is important to keep in mind which type of operation is being advocated, or is done "routinely." Smith,¹ in 1940, reported a series of 1,200 hysterectomies, using the same morbidity standard we have used here. He found a morbidity rate of 34 per cent for the entire series with a morbidity rate of 46 per cent for the total hysterectomy, and 28 per cent for the subtotal hysterectomy. His series showed a predominance of the subtotal operations. In clinics where the total operation is the one of choice, it is usually shown that the subtotal hysterectomy has a much higher mortality and morbidity rate. McDonald² in reporting 2,773 hysterectomies, in which 94.4 per cent were total hysterectomies, shows a mortality rate of 1.02 per cent for the total hysterectomy, and a mortality rate of 2.75 per cent for the subtotal. The reason for this is probably that in these clinics the subtotal operation is done only in those patients where the total operation is not feasible due to technical difficulties. Hence, nearly all of their subtotal operations are of Grades 3 and 4, in which the morbidity rates are much higher. The converse is often true in clinics where the subtotal hysterectomy is the procedure of choice, and the total operation is done only in those patients where there is enough cervical pathology to demand its removal. Dupertius and Zollinger,³ in reporting 1,000 cases from a general surgical service where 73 per cent of the operations were the subtotal hysterectomy, show a mortality rate of 4 per cent for the total operation, and 1.6 per cent for the subtotal operation. Their report includes a survey of the literature in which the subtotal operation is the predominant procedure, and in 16,851 hysterectomies the mortality rate was 2.4 per cent for the subtotal operation, and 4.1 per cent for the total hysterectomy. As a result of such discrepancies, it is important to compare the difficult subtotal operations with the equally difficult total hysterectomies.

The close parallelism between the morbidity rate of the colored and service patients is to be expected (Table II). Although there were many private colored patients, the majority were service patients. The high morbidity rate found in these two groups is due to the high percentage of "residues" of tubal disease. The increased percentage of "residues" means more extensive pathologic involvement of surrounding tissues in the pelvis, and, hence, the operations were found to be in the grades which carry the high morbidity rates.

Routine appendectomies are not done on this service. We do not think that the benefit gained by the so-called "prophylactic" appendec-

tomy is warranted when surgical principles must be violated. We believe that disease found in the appendix and a history of recurrent appendicitis are the indications for its removal. We feel that our series of appendicities removed is far too small to justify any claims as to the advisability of removing the appendix at the time of other surgical procedures in the abdomen. No statement other than our policy in this regard can be made.

In regard to the relation of pathology to the morbidity rate (Table V), it is interesting to note the even distribution of the morbid patients in the subtotal group. The patients with "residues" are the highest. One would expect the tumors without "residues," adhesions, or endometriosis to show the lowest morbidity rates, for these are the simplest types of operations from the technical standpoint. In the presence of previous pelvic infections, one would expect a higher morbidity rate due to the more difficult procedure involved, plus the fact that there may be latent deposits of bacteria which are activated by surgery. This assumption is more clearly shown in the total hysterectomy group. In the patients who had nothing more than a previous abdominal operation to complicate their picture, we find the morbidity rate near the general average. As there is presumably no previous infection factors in these patients, it would seem that the presence of previous infection and inflammatory processes are an important factor in raising morbidity.

All patients with a known or presumed malignancy were subjected to total hysterectomy. Complicated surgical procedures were necessitated by varying degrees of invasion and metastases, which accounts for the high percentage of morbidity in these groups.

In the group classified under "undetermined" pathology the morbidity rate is near the general average, which shows that even in the presence of minimal technical difficulties there is a rather high morbidity rate as measured by present standards. That is, the hysterectomy per se carries with it a certain morbidity rate, and potential mortality which cannot be dismissed. It is also interesting to note that in the patients who had endometriosis, which many times presents a most complicated technical picture, the morbidity rate was near that of the general average.

The distribution of the causes of morbidity in the grades of operations shows very little variation (Table IV). Most important is the occurrence of pulmonary embolism. Ten of the eleven in the series occurred in Grades 1 and 2. It is of interest to note that 4 of the 5 fatal instances of embolism, and 8 of the 11 in the series were in colored patients. Nearly twice as many instances of embolism occurred in the subtotal operation as in the total. All patients with pulmonary embolism were treated with intravenous papaverine, atropine, and oxygen.

The 26 patients who had local and wound infections constitute a separate group in which there was drainage and true infection. Most of these patients followed a characteristic course. The drainage began on the fifth to the tenth postoperative day and paralleled the temperature rise in amount and duration. The length of the operation, the difficulty of the procedure, the presence of infection, and the trauma to the tissues were all factors in producing these infections. They constitute 9.58 per cent of all the morbid patients.

Urinary tract infections account for 43 per cent of the identified morbidities, and 8 per cent of the patients had "infected" urine without a rise in temperature. This institution has always been conscious of the importance of "residual" urine, and all of the patients were on

a catheterization routine with this factor uppermost in mind. The etiologic factors of these urinary infections and possible theories as to their elimination is the subject of a subsequent report.

The "unknown" morbidities form an interesting group which demands considerable discussion. It was found that this group followed a definite temperature pattern in most instances. The temperature rises in this group are thought to be within the physiologic expectancy, and consequently are not true morbidities. The fact that these patients made an uneventful recovery, and did not have any positive laboratory findings seems to show that these patients did not have actual pathologic morbid conditions. We have thought that the term "physiologic morbidity," or "physiologic reaction," as compared to "pathologic morbidity," would be a better way to distinguish them. However, there were in this group a certain number of pathologic conditions of unknown etiologies.

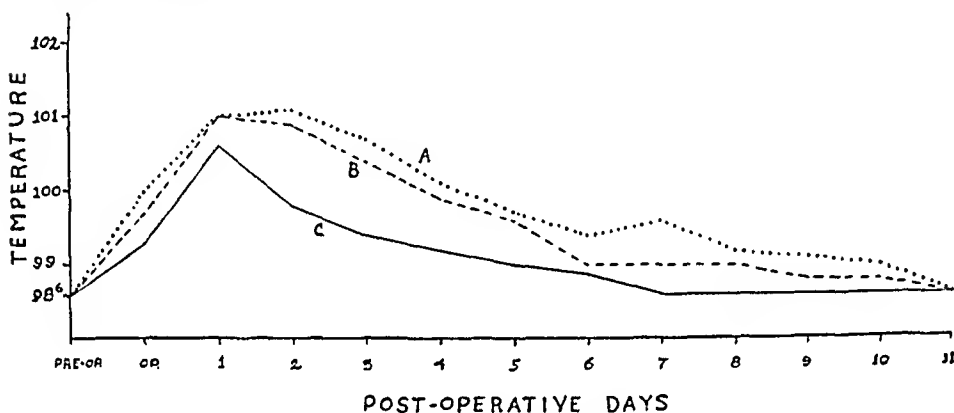


Fig. 1.—This shows a composite temperature curve of (A) 50 total hysterectomies, and (B) 50 subtotal hysterectomies from the "unknown" morbidity group. These patients are considered "physiologic" morbidities. Curve (C) shows 50 total and subtotal hysterectomies which were nonmorbid according to the standard used in this presentation.

Fig. 1 shows a composite temperature curve of 50 total hysterectomies and 50 subtotal hysterectomies that were in the "unknown," or "physiologic," morbid class. The lower curve shows a composite temperature curve of 50 nonmorbid total and subtotal hysterectomies. This latter group is nonmorbid by our present standard. We do not believe that the temperatures represented by the two upper curves are true morbidities. Table IV shows that 72 per cent of the patients became morbid on the first two days after surgery, and that 50 per cent of the patients were morbid for two or three days according to the standard used here. This further substantiates and augments the belief that these are not pathologic temperature curves. We do not feel that every patient with a temperature curve that falls above this average is morbid, but we do feel that in a study of a large series of operations the temperature curves that fall above this composite will be pathologic in nearly every instance, and an etiologic factor can be found for the morbid condition. Again let us state that the need for a morbidity standard is not only to judge the individual patient's postoperative course, but to study large groups; to analyze and to compare.

An intensive search of the literature has failed to produce a standard for surgical morbidity that has been accepted by any major surgical organization. Beck,⁴ in 1939, urged that the surgical societies establish

a morbidity standard as the obstetricians have done. Hunt⁵ urged repeatedly for careful analysis of surgical complications and deaths, but not for an actual morbidity standard.

We feel that to make such a standard workable, studies similar to this one should be undertaken for each of the more common surgical procedures, and in this way differentiate between "pathologic" and "physiologic" conditions. These would vary greatly in different operations.

Summary and Conclusions

1. An analysis of 800 abdominal hysterectomies is presented, and the incidence, factors, and etiology of morbidity involved are discussed.

2. The morbidity rate for the total hysterectomy was slightly higher than that for the subtotal operation, while the mortality rates for each procedure were approximately the same in this study.

3. Difficult technical procedures increased morbidity.

4. "Residues" of pelvic infection increased morbidity.

5. Urinary tract infections caused 43 per cent of the identified morbidities.

6. A differentiation between "physiologic" and "pathologic" morbidity must be made when temperature and time are used as a standard for morbid conditions.

7. A composite temperature curve of 150 hysterectomies is offered as a guide for differentiating the "physiologic" from the "pathologic" temperature rises following surgery.

8. Since there are no standards for surgical morbidity which are adequate for present-day needs, they should be established for each of the more common surgical procedures.

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Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY 12, 1943

The following case report and paper were presented:

Case Report: An Anomaly of the Sacrum Complicating Pregnancy. Dr. Hervey C. Williamson.

A Further Contribution to the Syndrome of Fibroma of the Ovary With Fluid in the Abdomen and Chest, Meigs' Syndrome. Dr. Joe Vincent Meigs of Boston (by invitation). (For original article, see page 19.)

MEETING OF FEBRUARY 9, 1943

The following case report and paper were presented:

Case Report: Accessory Hypoplastic Kidney and Ureter, Clinical Study and Operation. George F. Hoch, M.D. (by invitation), and William T. Kennedy, M.D.

Paper: Eclamptic Toxemia With Special Reference to Etiology. Herman W. Johnson, M.D., Houston, Texas (by invitation).

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF NOVEMBER 5, 1942

The following papers were presented:

Acute Intestinal Obstruction Due to Bands Complicating Pregnancy. Frank B. Block, M.D., and Phoenix M. Sales, M.D. (For original article, see page 134.)

The Importance of Focal Infection in Obstetrics. Myer Solis-Cohen, M.D. (by invitation).

An Attempt to Correlate the Pre-Eclamptic State With a Congenital Anomaly of the Kidney. Robert M. Hunter, M.D.

MEETING OF DECEMBER 3, 1942

The following paper was presented:

Favorable Response of Advanced Endometriosis to Testosterone Propionate Therapy. John C. Hirst, M.D. (For original paper, see page 97.)

MEETING OF JANUARY 7, 1943

The following papers were presented:

- Two Cases of Congenital Anomalies of the Gastrointestinal Tract, with Autopsy Findings.** Paul Morris, M.D., (by invitation).
- Early Pseudomyxoma Peritonei in a Case of Fetal Meconium Peritonitis.** Raphael Lattes, M.D., (by invitation). (For original article, see page 149.)
- Hypothyroidism as a Problem in Women, Second Report.** Carl Henry Davis, M.D. (For original article, see page 85.)
- The Simpson Operation in the Treatment of Uterine Retroflexion.** John B. Montgomery, M.D.
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CHICAGO GYNECOLOGICAL SOCIETY*MEETING OF DECEMBER 18, 1942*

The following paper was presented:

- Early Stages in Human Development With Special Reference to the Pre-Villous Ovum.** Arthur T. Hertig, M.D., Boston, Mass. (by invitation). To be published in a later issue.

MEETING OF JANUARY 15, 1943

The following papers were presented:

- The Effect of Complementing the Diet in Pregnancy With Calcium Phosphorus, Iron, and Vitamins A and D.** Fred L. Adair, M.D., William J. Dieckmann, M.D., and (by invitation) Herbert Michel, M.D., Florence Dunkle, M.S., Sylvia Kramer, Ph.D., and Edna Lorang, B.S. (For original paper, see page 116.)
- Studies of Surgical Morbidity: I. Abdominal Hysterectomy.** Harold O. Jones, M.D., and (by invitation), Leo W. Doyle, Jr., M.D.

Department of Reviews and Abstracts

Selected Abstracts

Abortion

Caffaratto, T. M.: A Rare Case of Massive Decidual Expulsion Following a Five Months' Abortion, *Ginecologia* 6: 229, 1940.

The author describes a case of massive decidual expulsion following an abortion in the fifth month of pregnancy. He demonstrates, in 9 photomicrographs, a moderate inflammatory change in the decidual tissue. The accompanying of a placenta marginalis, similarly involved, suggests to the author that inflammation of a low-implanted placenta may well explain the etiology of this massive decidual expulsion.

CLAIR E. FOLSOME

Dunn, Halbert L.: Frequency of Abortion, Its Effects on Maternal Mortality Rates, Vital Statistics, Dept. of Commerce, Bureau of the Census, Special Reports 15: 431, 1942.

Dr. Dunn, in this paper presented at the Conference on Abortion Problems, sponsored by the National Committee on Maternal Health, in June, 1942, at New York City, states that the frequency of abortion, as it effects maternal mortality rates cannot be determined without a very intensive, as well as extensive, study which does not appear feasible at this time. However, rough approximates indicate that about 50 per cent of the deaths from abortions are tabulated in the mortality statistics as such.

The number of deaths from abortions, in the United States in 1940, has been estimated to be between 3,000 and 4,000 in number. This figure constitutes about 30 to 35 per cent of maternal deaths from all causes. The general rates for causes of maternal death has been decreasing but the death rate from abortions has probably remained unchanged.

By using three arbitrary constants: (1) of 1 abortion to every 5.6 confinements for the urban areas; (2) of 1 abortion to every 9.4 confinements for the rural areas; and (3) assuming the fatality rate from abortion to be 1 per cent, it is possible to calculate the number of abortions and abortion fatalities. The estimated number of annual urban abortions was 188,393; rural abortions, 143,936 with a total of 332,393 per year, in this country. The annual fatalities from abortion can be estimated as about 3,300 in number.

One common source of error in mortality statistics on abortion is due to the confusion regarding the definition of the term "abortion" among the States, whether lunar or of calendar month basis, whether a five or seven months' time period differentiates abortion from "age of viability," "stillbirth," and premature death. The reporting habits of the physicians constitute another common source of error.

Dr. Dunn's article contains 5 excellent reference tables and 3 valuable charts which go far to crystallize the multiple complexities of statistics on the abortion problem. Copies of this article can be obtained from the Bureau of the Census, Washington, D. C.

CLAIR E. FOLSOME

Rutherford, Robert N., and Mezer, Jacob: Regeneration of Uterine Mucosa After Spontaneous Abortion and Normal Delivery, J. A. M. A. 119: 124, 1942.

Twenty-five cases were included in this study. The program of regeneration follows that laid down by Williams in his monograph on this subject. The authors showed that patients who are lactating regenerate the endometrium at approximately the same rate as the nonlactating patients. However, if ovulation is inhibited as by continued lactation, the endometrium tends to remain as resting or mildly proliferating endometrium, until at last the previous ovarian rhythmicity breaks through.

A similar process was repeated in cases of spontaneous abortion. It was found that the endometrium regenerates more rapidly and menstruation ensues quicker in cases where thorough curettage follows the abortion. Routine curettage is therefore recommended in cases of spontaneous abortion, even though all products of conception have been identified as extruded. Patients may be urged to seek impregnation within two weeks after spontaneous abortion. Following a normal full-term pregnancy, the patient is susceptible to impregnation after six weeks, although lactation may inhibit ovulation for a longer period of time.

WILLIAM BERMAN

Leon, Juan: Simultaneous Therapeutic Abortion and Sterilization (Value of Surgical Methods by the Vaginal Route), Arch. de la clin. obst. y ginec. 1: 113, 1942.

Leon presents the conclusions of a longer paper which appeared in *La Prensa Medica Argentina* in 1941. The question whether sterilization should be performed simultaneously with abortion or delivery frequently arises. Many obstetricians do a salpingotomy along with curettage while others prefer to wait several days or even weeks after the abortion. The same problem arises in connection with delivery at term. Some (Ottow and Anselmino) advise Menge's operation within twenty-four hours of delivery to avoid a second hospitalization and because the wounds heal better during the involution period. Eymer advises delay until the third or fourth day, while Engelman believes that dangers of infection are greater during this period and prefers to wait six weeks. With this procedure the patient may become pregnant again. However, in such cases curettage may be done a few days after sterilization if the Friedman test is positive. Perhaps the best way is to keep the patient in the hospital for the six weeks' period, although the attendant expense and the long absence of the woman from her home are definite drawbacks.

The author concludes that at the present time there are not many indications for vaginal surgery in simultaneous abortion and sterilization. The need for vaginal surgery has been reduced for several reasons: speed is not considered as essential as safety; in the first two months of pregnancy there is no necessity for supplanting the current obstetrical practices of dilating the cervix and curettage; tubal sterilization by colpotomy is more dangerous during pregnancy than later; x-rays, radium and other biologic methods of sterilization are available.

The need for vaginal surgery occurs principally in the third month of pregnancy when uterine evacuation by obstetric methods is difficult and dangerous because of the size of the pregnancy and because simple rupture of the amniotic sac is not practicable.

There are four techniques for vaginal "minor" cesarean sections: vaginocervical-lower uterine segment, vaginolower uterine segment with longitudinal incision, vaginolower uterine segment with transverse or arciform incision, and vaginocorpus. The last three are generally preferred since the cervix is not involved. These different types of hysterotomies can be combined in the same operation with any of the methods of tubal sterilization, permanent or temporary.

If the least operative trauma is desired in a patient in poor condition, and especially if the pregnancy is a little advanced, sterilization should be deferred. If the cervix is infected, opening the peritoneal cavity to perform a sterilization constitutes a definite and serious danger. In such circumstances, if a surgical method is necessary, cesarean section by the vaginocervicolower uterine segment or vaginolower uterine segment routes is preferable, the latter especially when cervicitis is present, leaving until later sterilization by colpotomy or other surgical (Menge, Stoeckel) radiation or biologic methods. Abdominal hysterotomy may be combined with sterilization.

J. P. GREENHILL

Wenner, R.: The Significance of a Successfully Overcome Threatened Abortion on the Subsequent Course of Labor, Monatschr. f. Geb. u. Gynäk. 112: 325, 1941.

A review of the literature reveals that if pregnancy continued after threatened abortion there was a decided increase in premature deliveries and complications during labor. Furthermore, more deformed babies were born and many of the babies later proved to be inferior intellectually and physically. The author investigated 92 cases of threatened abortion where the abortion was prevented. Premature labor occurred in this series in 23.9 per cent as opposed to the usual incidence of 16.2 per cent. Only one deformed baby was delivered in his series. Operative deliveries were necessitated twice as frequently as usual. Complications on the part of the placenta were greatly increased. The author concludes that with the present form of therapy, abortion may be prevented and healthy babies obtained.

J. P. GREENHILL

Benthin, W.: Prognosis and Possibilities of Modern Therapy of Febrile Abortion. Geburtsh. u. Frauenh. 2: 393, 1940.

According to W. Benthin, complications are to be anticipated in approximately 15 per cent of febrile abortions. The mortality rate is 7 per cent, much higher than in febrile puerperal states. Of patients with parametritis infections at the time of hospitalization, 31 per cent die. A considerable number remain sterile, and those with primary recovery may develop later sequelae. Expectant treatment offers best results in cases in which infection is confined to the uterus. Spontaneous expulsion takes place under expectant treatment in from one-sixth to one-third of the cases. Quinine and ergotamine tartrate promote the expulsive efforts, especially if used with vaginal tamponade. This tamponade stimulates uterine contractions and prevents excessive loss of blood. The use of carbon dioxide applied within the uterus and of the ice bag are valuable in restricting the infectious process to the uterine cavity. Early medication with sulfanilamide is advisable for prevention and arrest of general septic infections and in peritonitis. The expectant treatment requires strict rest in bed. A well-planned expectant treatment prevents sepsis and pyemia and parametritis infections. Operative evacuation of the uterus can be tried without much danger five days after the fever has subsided. An earlier or immediate surgical evacuation is permissible only in extremely urgent cases. There exists no vital indication for operative evacuation as long as the cervical canal is still closed. This should be kept in mind, especially in the presence of parametritis, peritonitis and inflammations of the adnexa. If the cervical canal is open and if severe hemorrhage exists, intervention is permissible, and if placental parts are already undergoing expulsion, their removal is indicated. The digital method is the most reliable and least harmful. It should be performed with deep anesthesia and as carefully as possible. Introduction of carbon into the evacuated uterus promotes detoxication and rapid discharge of secretions. Azosulfamide, dextrose, continuous infusions, administration of vitamins, and blood transfusion are the most important aids in the treatment of infection. All febrile abortions should be treated in a hospital.

J. P. GREENHILL

Uttley, K. H.: After-Histories of the Pregnancies of Over 3,000 Chinese Multigravidae in Hong Kong, Chinese M. J. 59: 543, 1941.

A statistical investigation has been made into the histories of 3,134 consecutive Cantonese multigravidas attending an antenatal clinic in Hong Kong. All such patients were questioned as to what had happened to their previous pregnancies, how the pregnancies had terminated, and what had happened to the children subsequent to delivery and up to the time of this investigation. The results are tabulated for each group of gravidas. The finding was that no matter what group of gravidas one dealt with, the miscarriage rate was approximately 7 to 12 per cent, the infantile and childhood death rate (including stillbirths) was 30 to 35 per cent, and the percentage living was 58 to 65 per cent.

C. O. MALAND

Dietel, H.: Technic of Removal of Uterine Mole, Zentralbl. f. Gynäk. 64: 1050, 1940.

Dietel discusses the risks of infection and perforation in the usual methods of removal of uterine mole as well as the danger of leaving fragments behind. He uses a special blunt curette, 36 cm. long with a loop of 35 mm. width, 8 mm. high. In order to thicken the uterine wall, posterior pituitary extract is given intravenously just before beginning curettement and a hand is kept over the fundus to help maintain contraction. As a diagnostic aid Dietel points to the very rapid sedimentation of the blood in the first hour alone. In his series of 10 cases sedimentation in the first hour was from 8 to 78 mm. with an average of 40 mm.

R. J. WEISSMAN

Schultze, K. W.: Fetal Congenital Abnormalities, Their Cause and Clinical Significance, Ztschr. f. Geburtsh. u. Gynäk. 121: 242, 1940.

The literature dealing with germ plasm deficiency as a cause of abortion is discussed at length and an estimation made of its application to the practical social problem of abortion in Germany. Philipp is quoted as estimating that for the 1.3 million births per year in "Old Germany" (Altreich) there are 220,000 abortions. The various nonhereditary disturbances in the mother are discussed with special stress laid upon corpus luteum deficiency. Various statistical expressions (His, Mall, etc.) are presented and a final estimate made that one abortion due to germ plasm deficiency may be expected for every 13 live births. This alone would account for 100,000 of the estimated number of abortions.

The author states that criminal abortions have decreased by 80 per cent in the Altreich in recent years. He also estimates that abortions due to treatable causes were decreasing in a group of European countries before the present war. This gradually increased the proportion of abortions due to germ plasm deficiency, and references are given to studies which have supported this. Since many of the hereditary lethal combinations which cause abortion are sex linked and the vast majority of such abortions which occur in the first four months of pregnancy affect male fetuses (Fig. 4, p. 260), an increase in the percentage of males aborted will indicate a decrease in other causes of abortion than germ plasm deficiency. This apparently was occurring before the war.

A plea is made for more careful and complete examination of abortion material in order that more accurate information may be obtained.

An excellent bibliography is attached.

J. L. MCKELVEY

Winkler, H.: *The Active Treatment of Febrile Abortion, Also a Contribution to the Question of Secondary Sterility*, München. med. Wchnschr. 87: 1052, 1940.

Dr. Winkler states that there is today no uniform treatment of "septic uncomplicated abortion" (fever but no inflammatory changes of the para- and perimetrium or of the pelveoperitoneum). He favors the active treatment and gives a statistical study of 158 cases of febrile abortions treated from July, 1933, to July, 1940. One hundred and thirty-eight were treated radically (4 deaths), 7 conservatively (1 death), and 13 by a combination of both (no deaths). In competent hands he claims that the active treatment of febrile abortions, by disinfecting the uterine cavity with an Iodine solution, has three advantages: (1) lowered mortality, (2) shorter stay in the hospital and a quicker convalescence, (3) and only a small percentage of the patients became sterile.

C. E. PROSHEK.

Vogt-Møller, P.: *The Therapeutic Application of Vitamin E in Human Abortions*, Acta. obst. & gynec. Scandinav. 20: 85, 1940.

A survey of the therapeutic application of vitamin E is made by Vogt-Møller who found that vitamin E has proved to be most valuable in the treatment of habitual abortion. In a series of cases this vitamin successfully prevented abortion in from 75 to 80 per cent of the cases. Likewise, vitamin E has been successful in cases of threatened abortion, premature separation of the placenta, and toxemias of pregnancy. On the other hand, this vitamin has proved useless in cases of primary and secondary sterility, amenorrhea, dysmenorrhea, menorrhagia, and genital hypoplasia and the menopause.

In some cases of irregular glandular hyperplasia, vitamin E has yielded favorable results.

The author points out the relationship between vitamin E and the sex hormones, particularly progesterin. He also emphasizes the possible beneficial effect of vitamin E in the treatment of some neurologic disorders.

J. P. GREENHILL.

Collins, Conrad G., Weed, John C., and Collins, Jason H.: *The Treatment of Spontaneous, Threatened, or Habitual Abortion*, Surg., Gynec. & Obst. 70: 783, 1940.

Wheat germ oil therapy forms a valuable basis for the treatment of spontaneous and/or habitual abortion.

Wheat germ oil therapy should be fortified by the administration of progesterin and/or thyroid extract when necessary.

The fear of delivering a malformed fetus in cases in which spontaneous or habitual abortion has been successfully combatted is over-emphasized.

All efforts should be made to control spontaneous abortion or habitual abortion by the use of all known remedies which have been proved of value.

The results in 36 patients so treated were presented to substantiate these views.

WILLIAM C. HENSKE.

Anwandter, K.: *Metrorrhagia Probably Due to Avitaminosis*, Bol. Soc. chilena de obst. y ginec. 5: 3, 1939.

The author reports the similar cases of two women aged 28 and 25 years, respectively, both with postabortive bleeding due to retained decidua after light curettage. A few days after the second curettage each patient had profuse metrorrhagia. Calcium chloride, auto-hemotherapy, vasoconstrictors, and other

therapy was tried without success. Hemorrhage in each case ceased shortly after an injection of vitamin C. In the discussion, the lack of controlled studies to establish the fact of a hypovitaminosis was pointed out. It was also claimed that vitamin C was effective in controlling melena neonatorum.

R. J. WEISSMAN.

Jeffcoate, T. N. A.: Missed Abortion and Missed Labour, Lancet 238: 1045, 1940.

Intrauterine death of the products of conception is followed by a decrease in the amount of estrogen in the blood stream. Administration of estrogens to patients with missed abortion and missed labor so increases the sensitivity of the uterus that its evacuation is usually promoted. The method of induction described here was successful in 48 out of 55 consecutive cases. Expulsion of the products of conception was free from complications, such as uterine hemorrhage and infection.

Fourteen cases were treated with estrone or estrone benzoate, 30 with estradiol benzoate, and 11 with stilbestrol. The following technique is suggested: Estradiol benzoate is given intramuscularly in a dose of 2 mg. every eight hours for seven or eight days. If abortion has not taken place by the fifth day, 10 gr. of quinine hydrochloride are given each hour for three doses and followed by four injections of 0.5 c.c. of posterior pituitary extract at intervals of an hour. This treatment is repeated on the eighth day if the products of conception still remain in the uterus. When stilbestrol is used instead of estradiol benzoate, 2 mg. are given by mouth thrice daily, or 1 mg. every four hours, for seven or eight days. The quinine and pituitary extract are also given when required on the fifth and eighth days.

Induction of labor was successful in 28 of 29 patients beyond twenty-eight weeks of pregnancy, and in only 9 cases were accessory uterine stimulants necessary. It was successful in 20 to 26 cases before twenty-eight weeks, but quinine and/or pituitary extract was used in 11.

CARL P. HUBER.

Opazo, Victor: Postabortive Metastatic Panophthalmitis, Bol. Soc. chilena de obst. y ginec. 4: 199, 1939.

A 40-year-old multipara, 3-months pregnant, took quinine and aborted. Severe hemorrhage followed and a curettage was performed. The following day she presented general signs of infection, and that same afternoon she suddenly lost her vision. On examination the right eye appeared swollen but was painless. The vitreous soon became purulent. There was intense edema of the upper eyelid.

Treatment consisted of sulfanilamide, uterine tonics, and vaginal douches. The eye was enucleated with subsequent recovery of the patient. No mention is made of recovery of vision in the opposite eye. Discussing various theories of the etiology of the ophthalmitis, the author concludes that the most important thing is the differentiation from gonococcal conjunctivitis. Absence of the Neisserian organism, absence of purulent conjunctivitis and pus in the anterior chamber or vitreous along with protrusion of the globe and limitation of its mobility are the essential diagnostic points.

R. J. WEISSMANN.

Yero Bou, E., and De La Vega, A. M.: Treatment of Septic Abortion, Rev. cubana de obst. y ginec. 1: 117, 1939.

The authors reviewed 415 cases of incomplete abortion on their service. Curettage was practiced in 285 cases; 34 did not go on to complete abortion and medical treatment alone was given the remaining 96 cases. Of those curetted, 42.5 per cent were febrile on admission. Comparing immediate to deferred curettage, the authors found no complications if the operation was done on an afebrile patient.

In a special ward 37 infected cases were studied. Twenty-two improved without intervention. Sulfanilamide, ergotamine tartrate and general supportive measures were employed. Of the remainder, 2 had immediate curettage for acute hemorrhage and 13 were curetted after an average of 3 afebrile days. All patients in this group of 37 confessed to chills and high fever at home and many had been criminally aborted. The average stay in the hospital was eight days.

R. J. WEISSMAN.

Ortiz, N. C.: Considerations in the Treatment of Uterine Perforation, *Rev. méd. latino-am.* 25: 276, 1939.

The percentage of surgical perforations varies from 0.5 per cent to 1.5 per cent. In the author's clinic, over 500 curettages were performed, with 4 perforations. Four case histories are given, one of a fatal case involving several intestinal perforations. Ortiz feels that expectant treatment should be followed in simple perforation in the absence of signs of infection or lesions of the other viscera. All others should be subjected to laparotomy, reserving the vaginal approach for exceptional cases. Intestinal lesions should be carefully searched, even though the patient does not appear to be toxic. Whenever possible the uterus is sutured and ovaries are preserved. The fundus is amputated if necessary. Gangrene of the uterus is the author's only indication for total or subtotal hysterectomy in this condition.

R. J. WEISSMAN.

CORRESPONDENCE

To the Editor:

In the January issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, there is an article by Drs. Milton Goodfriend and Mark Daniel on the Kapeller-Adler test in the diagnosis of pregnancy. They state that the American literature in the past decade contains little reference to this test.

I wish to call attention to the fact that the writer together with Dr. I. B. Oldham, Jr., and Mr. T. J. Dunn published an article in the *Oklahoma State Medical Journal*, Volume 30, Number 6, June, 1937, relative to this test.

We reported a series of 215 cases, some of which were checked with the Friedman test. We arrived at the following conclusion: The specimen should have a specific gravity of at least 1.020 but heavier concentration is better. Either the test is positive or negative; there is no middle ground. There should be some definite standard of determination of positive and negative results similar to a Sahli colorimeter. The test in our hands has proved to be a fairly accurate one; it is easily and rapidly done. However we do not feel that this test can replace the Aschheim-Zondek or the Friedman modification.

We have continued to use this test since the publication of the above-mentioned article with approximately the same result as to accuracy.

CHARLES ED. WHITE, M.D.

March 6, 1943
Muskogee, Okla.

Necrology

ARTHUR WALTER BINGHAM, obstetrician, gynecologist, and civic leader, died at his home in East Orange, New Jersey on May 19, 1943, at the age of 71. Organized and directed the obstetric department of the Orange Memorial Hospital, was past president of the Academy of Medicine of Northern New Jersey, long known for his outstanding activities in maternal welfare work in his state. He graduated from Cornell University in 1893 and from the College of Physicians and Surgeons of Columbia University in 1896.

JAMES EWING, one of the world's foremost authorities on cancer and a pioneer in radium treatment of that disease, died in New York City, May 16, 1943, at the age of 76. He was professor of oncology at the Cornell Medical College, and consulting pathologist to various hospitals. He devoted much time to research on cancer treatment and to the development of the Memorial Hospital in New York, of which he also served as director for many years. Author, teacher, scientist, traveller, he was the recipient of many honorary degrees. Among his earlier contributions to the literature were observations and studies on eclampsia, especially the effects on the liver. Dr. Ewing was a graduate of Amherst College in 1888 and of the College of Physicians and Surgeons of Columbia University in 1891.

Item

American Board of Obstetrics and Gynecology, Inc.

The annual meeting of the Board was held at Pittsburgh, Pennsylvania, from May 20 to May 25, 1943, at which time one hundred and eight candidates were certified.

A number of changes in Board regulations and requirements were put into effect. Several of these changes are designed to broaden the requirements for candidates in Service. Examples are the allowance of a stipulated amount of credit toward special training requirements for men in Service and assigned to general surgical positions, special training allowances on a preceptorship basis for men assigned to obstetric or gynecologic duties in military hospitals and working under the supervision of Diplomates or recognized obstetrician-gynecologists, as well as credit toward the "time in practice" requirement of the Board to be allowed for time in Military Service.

The Board will no longer require a general rotating internship, but will now accept a one-year intern service, although the rotating internship is preferable. Such services must be in institutions approved by the Council on Medical Educa-

tion and Hospitals of the A. M. A. Lists of such institutions are published regularly in the Educational Number of *The Journal of the A. M. A.*

The privilege of reopening applications by candidates who have been declared ineligible has been extended to two years from date of filing the application, instead of one year.

The Board has ruled temporarily to excuse men in Military Service from the submission of case records at the stipulated examination times, thereby permitting them to proceed without further delay with the Board examinations. This does not obligate the Board, however, to waive the case record requirement for such candidates. Plans have been made to provide similarly for Service men upon their eventual discharge from the Armed Forces, and to permit the greater use of operations done while in residency or in civilian practice before the War.

The next Part I examination of the Board (written paper and submission of case records) will be held on Saturday afternoon, February 12, 1944, at a place convenient to the location of the candidate, whether he be in civilian or military life. Applications must be in the Office of the Secretary by November 15, 1943, ninety days in advance of the examination date. The time and place of the Spring 1944 (Part II) examination will be announced later.

Prospective applicants or candidates in Military Service are urged to obtain from the Office of the Secretary, a copy of the "Record of Professional Assignments for Prospective Applicants for Certification by Specialty Boards" which will be supplied upon request. This record was compiled by the Advisory Board for Medical Specialties and is approved by the offices of the Surgeons-General, having been recommended to the Services in a circular letter, No. 76, from the War Department Army Service Forces, and referred to as the Medical Officers Service Record. These will enable prospective applicants and candidates to keep an accurate record of work done while in Military Service and should be submitted with the candidate's application, so that the Credentials Committee may have this information available in reviewing the application.

Applications and BULLETINS of detailed information regarding the Board requirements will be sent upon request to the Secretary's Office, 1015 Highland Building, Pittsburgh, Pennsylvania.

Examinations

Applications for the 1944 examinations of the Board are being received at the office of the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, Pennsylvania. Booklets of information regarding Board requirements and examinations, together with application forms, will be sent upon request.

All applications for the year 1944 must be in the Secretary's Office not later than November 15, 1943, ninety days in advance of the Part I examination date.

Candidates are required to take both the Part I and Part II examinations. The Part I examination consists of the written paper and the submission of twenty-five case history abstracts, and will be conducted on Saturday, February 12, 1944. This examination will be arranged so that the candidate may take it at or near his place of residence. Upon the successful completion of the Part I examination, candidates are eligible for the Part II examination consisting of a pathology and an oral examination. This is given at the annual meeting of the Board once each year, the time and place of which will be announced later.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they request orders to "detached duty" for the purpose of taking the examinations whenever possible.

PAUL TITUS, M.D.
Secretary.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society. *President*, George W. Kosmak, New York, N. Y. *Secretary*, H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Annual meeting cancelled.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting, September, 1943, Hot Springs, Va.
- Central Association of Obstetricians and Gynecologists. *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Annual meeting cancelled.
- South Atlantic Association of Obstetricians and Gynecologists. *President*, Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Annual meeting cancelled.
- A. M. A. Section on Obstetrics and Gynecology. *Chairman*, L. E. Phaneuf. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Annual meeting cancelled.
- New York Obstetrical Society. *President*, W. T. Kennedy. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia. *President*, Catharine Macfarlane. *Secretary*, James P. Lewis, 3815 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society. *President*, Edward Allen. *Secretary*, Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society. *President*, Samuel Lubin. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society. *President*, Lawrence Warton. *Secretary-Treasurer*, John W. Haws, 9 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society. *President*, Edward Friedman. *Secretary*, Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society. *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology. *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society. *President*, J. L. Gilmore. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston. *President*, Thos. Almy, Fall River, Mass. *Secretary*, Paul A. Young, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society. *President*, Frank A. Pemberton. *Secretary*, A. F. G. Egelow, 31 Maple Street, Springfield, Mass. Meetings held in May and December.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL

- Pacific Coast Obstetrical and Gynecological Society.** *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting undecided, probably San Francisco, Calif., November 5-6, 1943.
- Washington Gynecological Society.** *President*, John Warner. *Secretary*, L. L. Cockerille, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. Melver, 714 Medical Arts Building, Dallas, Texas.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, Norman F. Miller. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, J. M. Weldon, Mobile, Ala. *Secretary*, J. F. Williams, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutler. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** *President*, Glen N. Rotten. *Secretary*, R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.
- Denver Obstetrical and Gynecological Society.** *Secretary*, Emmett A. Meckler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** *President*, Geo. D. Huff. *Secretary*, Frank Russell, 233 A Street, San Diego, Cal. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** *President*, John D. Graham, Devil's Lake. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** *President*, H. C. Spalding. *Secretary*, W. C. Winn, 816 West Franklin St., Richmond, Va. Next meeting, October 26, 1943, Roanoke, Va.

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EXCRETION OF ESTROGEN AND GONADOTROPIN IN LATE PREGNANCY*†

With Especial Reference to the Toxemias of Pregnancy and
to Quantitative Methods

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THE etiology of the toxemias of pregnancy, especially pre-eclampsia and eclampsia, has remained obscure. Among the recent theories to be advanced have been those concerning the role of sex hormones. From extensive and detailed studies Smith and Smith¹⁻¹³ have concluded that the excretion of estrogen is low and that of gonadotropin high in pre-eclampsia and eclampsia and that "The close correlation between the clinical and hormonal findings and the fact that both abnormalities may be alleviated by estrogen and progestin administration (even though only temporarily in the severe pre-eclampsies) has led us to the conclusion that the clinical manifestations of pre-eclampsia are the direct result of a changed metabolism of sex steroids involving a greatly increased rate of destruction and accountable to estrogen and progestin deficiency."¹³ On the other hand Taylor and Seadron¹⁵ (1939) have concluded concerning the estrogens and gonadotropins that "the significance of these hormone differences between normal and toxemic patients is still a matter of theory," "that there was evidence of a frequent but not invariable lowering of the estrogen values in the toxemic cases and of an

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†Read, in part, at a meeting of the Chicago Gynecological Society, February 19, 1943.

elevation of prolan values in a few cases only," and that "the hormone changes observed in the toxemic patients are perhaps associated with the cause of toxemia but may simply be the result of disturbed kidney, liver or placental physiology." In general, our preliminary note¹⁴ and the reports of other workers corroborate the findings of low estrogen and high gonadotropin values. Reviews of the subject have been published by others.¹⁵

This investigation was undertaken in 1934 shortly after the first reports of Smith and Smith.^{1, 2} The purpose was to further the study of the relationship of hormones (estrogens and gonadotropins) to the toxemias of late pregnancy (1) by a rigid clinical classification of the material, (2) by pharmacologic assay of the hormones, and (3) by a statistical interpretation of the laboratory findings. At the time this work was begun pharmacologic assay on blood was impossible for toxemic patients because of the large amount of blood required for such an assay. Therefore, the problem was undertaken from the standpoint of the excretions of estrogens and gonadotropins. We realize the limitation of such an approach to the problem without the study of blood values and also the desirability of fractionation of the estrogens.

The classification used was that of the American Committee on Maternal Welfare:¹⁶

Group A. Disease not peculiar to pregnancy

I. Hypertensive disease

II. Renal disease

Group B. Disease dependent on or peculiar to pregnancy

I. Pre-eclampsia

II. Eclampsia

Because of the small number of cases Group A representing coexisting conditions was not subdivided in this study. Particular emphasis has been placed on the final diagnosis after postpartum observation in all cases.

Since, in 1935, quantitative methods of extraction of both estrogens and gonadotropins and their quantitative assay were in early stages of investigation considerable attention was given to the development of these procedures and the methods then adopted have been used throughout this study (1935-1940). Since the graded dose procedure commonly used for "quantitative" assay results in great discrepancy due to failure to split dosages with less than a 50 to 100 per cent or more variation, standard dose-effect curves were prepared for both substances. This obviated difficulties in splitting dosages and minimized the error due to biologic variations observed when small numbers of animals are used for biologic assays. Methods of extractions of both estrogens and gonadotropins were studied.

Even with pharmacologic assays variations in the amounts of hormone excreted are great not only between different patients but also between

different specimens of the same patient. There is also extreme overlapping of the individual values in the different classifications of patients. Thus it becomes very difficult unless a value is extreme to allocate it to a certain clinical group (Figs. 3 and 4). With such data averages often give erroneous and distorted results. Consequently, we have subjected our data to statistical analysis to test whether or not the differences observed in the mean values of the excretions of these hormones by the various groups are significant.

Casual inspection of our data suggested that there might be a relation between the amounts of estrogen and gonadotropin excreted by each patient, that is, a patient excreting a large amount of estrogen also tended to excrete a large amount of gonadotropin. To test this we have calculated the estrogen to gonadotropin ratio which is an arbitrary value dependent upon the units we have used but which seems to be a better index of hormone balance in individual cases than the twenty-four-hour excretion value of either estrogen or gonadotropin (Figs. 3 and 4).

In the course of the investigation the hormone excretions in other pathologic conditions of pregnancy have been studied.

Part I. Experimental Methods

1. EXTRACTION OF ESTROGENS AND GONADOTROPINS FROM PREGNANCY URINE

Estrogens.—After testing various procedures for the extraction and assay of estrogens from pregnancy urine, a method employing oil extracts was adopted. This method seemed advisable because of the well-known advantages of the administration of estrogens in oil and because the low excretion of estrogens by toxemic patients made concentration desirable. Various methods of hydrolysis of the urine were studied, in which both the acid concentration and period of hydrolysis were altered. The completeness of the extraction was also tested. Prolonged heating was employed to destroy androgens as well as to aid hydrolysis of conjugated estrogens. The estrogen was extracted with benzene for ten hours in a continuous extractor of the type designed by Gallagher, Koch and Dorfman,^{17, 18} and holding a 200 to 300 c.c. specimen. A calculated amount of olive oil was added to the benzene extract and the benzene removed in vacuo. We realize the advantages of the separation of various estrogens, but in order to keep the methods uniform throughout the study and to prevent loss of activity, no attempt was made to fractionate the estrogens or purify the extracts.

Gonadotropins.—In order to preserve the gonadotropins in the pregnancy urine until a pharmacologic assay could be made, the following method was adopted for use in this study:

A portion of the twenty-four-hour refrigerated specimen of pregnancy urine was acidified with concentrated HCl to pH 5.5 (nitrazine). Ten samples of 2 to 5 c.c. each were put into conical centrifuge tubes containing 5 volumes of 95 per cent ethyl alcohol (Zondek alcohol precipitation method). These tubes were stoppered and placed in the refrigerator overnight. They were centrifuged and the supernatant fluid discarded. The precipitate containing the gonadotropin was triturated with 95 per cent ethyl alcohol without removal from the tube, centrifuged and the

washing discarded. This procedure was repeated with anhydrous ether. The dry precipitate was stored in the tube in the refrigerator. When needed, individual preparations were triturated with the desired amount of water, centrifugated and the supernatant solution used for assay.

The reliability of this method of extraction is illustrated by a comparative assay of the extract and diluted urine. Two groups of 25 paired litter mate male rats (twenty-one days old) were used. In one group all the rats received a total dose of 0.03 c.c. pregnancy urine and in the other the extract equivalent to the same amount of urine. Both groups were injected 3 times daily for three days and antopsied at ninety-six hours. In the first group on urine, 45.5 per cent gave a positive response and 54.5 per cent gave a positive response on the extract. According to the assay method described below, this gives values of 31.7 and 35.3 R.U. per c.c., respectively, or an agreement of 90 per cent by the two methods. Additional assays using extracts gave values of 34.8 and 33.3 R.U. per c.c. These data were confirmed by other similar tests.

2. ASSAY OF ESTROGENS AND GONADOTROPINS

Estrogens.—The estrogens were assayed according to the dose-effect curve method proposed by Coward and Burn,¹⁹ D'Amour and Gustavson,^{20, 21} and other workers. This consists of preparing a curve from the percentage response on varying doses of estrogen and converting it into a dose-effect curve in which the amount of estrogen giving a 50 per cent response is considered as 1 R.U. Such a curve was established for our colony using 53 ovariectomized adult Wistar rats. All injections were made in olive oil. Later another curve was prepared using crystalline estrone standardized against International Standard Estrone.* The two curves were essentially the same and agreed well with those of other workers. However, the value of the rat unit differed as anticipated; 1 R.U. was equal to 29 I.U. of estrone which agrees in magnitude with Hain and Robson²² (33 I.U.), with Taylor and Seadron¹⁵ (35 I.U.) but not with Smith and Smith⁹ (5 I.U.), Burn and Elphick²³ (10 I.U.), or D'Amour and Gustavson²¹ (13 I.U.). Because the curves were to be used for routine assay purposes the general procedure in preparation was designed to meet a routine method and differed somewhat from those previously described by others:

Ovariectomized adult Wistar rats were used for the assay. Vaginal smears were made for two weeks prior to operation and any rats showing abnormal cycles were discarded. Ten days following the operation the rats were smeared for five days and then given an "excess dose" of estrogen (a dose high enough to give full cornification in 100 per cent of the rats). No selection was made for sensitivity of the rats to estrogen. Injections were made subcutaneously; all extracts were made in olive oil. The smears were read at forty-eight hours. A positive response was taken as a smear with a predominance of cornified epithelial cells. After a positive response the rat was not injected for two weeks. After a negative response the rat was used the following week. If negative again it was given an "excess dose" of estrogen. Consequently, no point on the curve was determined on a single day. This procedure was used in both the preparation of the curve and the assays. The curve was prepared by approximately half of the rats being given ascending and half descending doses of estrogen. In the crystalline estrone curve there were 98 rats on each of the 20, 30, 40 I.U. dose and 20 additional on the 20 I.U. point and 4 more at the 40 I.U. point.

*This material was supplied by the Abbott Laboratories, North Chicago, Illinois.

For assay purposes 4 to 10 rats were injected with graded doses of the unknown extract to ascertain the approximate value of one rat unit and the dose falling on the portion of the curve showing maximal sensitivity. At the dose thus determined groups of five ovariectomized rats were injected on each of four (or five) different days. The number of positive responses was totaled and the amount of estrogen equivalent to this percentage response was determined from the curve; from this the twenty-four-hour value was calculated in terms of equivalents of international units of crystalline estrone. Injecting small groups of rats on four or more days rather than the total number on one day seemed to minimize the error due to biologic variation commonly observed when duplicate assays are performed on different days. In future work this variation could be minimized by parallel assay of standard estrogen, as recommended by Hoskins, Coffman, Koeh and Kenyon,²⁴ and Burn.²⁵

Gonadotropins.—At the time this investigation was started neither a standard unit nor standard chorionic gonadotropin was available. Consequently, the values reported here unfortunately appear in biologic units of an arbitrary standard chosen by us.

Considerable time was spent in comparison of various methods of assay using ovary and seminal vesicle weight response, and the blood point response in the ovary of immature rats. The response of either the ovary or the seminal vesicle is sensitive to small doses of chorionic gonadotropin only over a very small range in the region of the minimal dose. Furthermore, the weight response of the seminal vesicle depends upon a general development of the organ while that of the ovary depends upon the formation of both follicles and corpora lutea and is also less sensitive. In fact, weights less than those of the control group are often obtained with minimal doses as observed also by Heller, Lauson, and Sevringhaus²⁶ with rat pituitary extracts and Cartland and Nelson²⁷ with pregnant mares' serum, by Gaensbauer and Bradbury²⁸ with commercial preparations and Sealey and Sondern²⁹ with "International Standard" gonadotropin. The blood point and corpus luteum response is often difficult to ascertain on low dosage without histologic examination, which becomes laborious for large numbers of assays.

A typical comparative experiment is shown in Fig. 1. Male and female rats strictly twenty-one days old and from 55 litters were treated with pregnancy urine at total dosage levels of 0.025, 0.05, 0.1, 0.2, 0.3, and 0.5 e.e. There were 25 males and 25 females on each point on the curve. In general from each litter used, one male and one female were placed on each of three points and one in each control group. The injections were made subcutaneously twice daily for three days and the rats sacrificed at ninety-six hours. The ovaries and seminal vesicles* were weighed on a Hartmann-Brann microtorsion balance and the blood point response in the ovaries noted. The value of a positive weight response in the ovaries and in the seminal vesicle was arbitrarily set as a value which exceeded the mean weight of these organs in the control groups by more than twice the standard deviation in these groups, a value which might be anticipated to be exceeded about one time in 44 in the untreated control group. The response of the S. V. to gonadotropin is shown by Curve A, of the ovarian weight by Curve B and of the blood point response by Curve C. At levels of 0.025, 0.05, 0.1, 0.2, 0.3, 0.5 e.e., the percentages of the positive responses of the seminal vesicles were 72, 100, 100, 100, 100,

*In dissecting the seminal vesicle, the adherent part of the coagulating gland was included.

and 100, respectively, of the ovarian weights 8, 8, 52, 56, 64, 75 per cent, respectively, and of the blood points 0, 72, 84, 52, 64, 56 per cent, respectively.

It is noted that at a total dose of 0.1 c.c. of pregnancy urine that the blood point response was 84 per cent, the ovarian weight response 52 per cent, and the seminal vesicle response 100 per cent. At the region of minimal dose and of maximal sensitivity the blood point response and seminal vesicle weight response are parallel. The region of maximal response to changes in dosage is at a very low level. Furthermore the percentage value is influenced less by an extreme value than the mean weight of the entire group would be. From this and similar experiments the seminal vesicle response was selected for our assay purposes. The reliability of the seminal vesicle weight response for assay of chorionic

QUANTITATIVE RESPONSE OF OVARIES AND SEMINAL VESICLES TO GONADOTROPIN

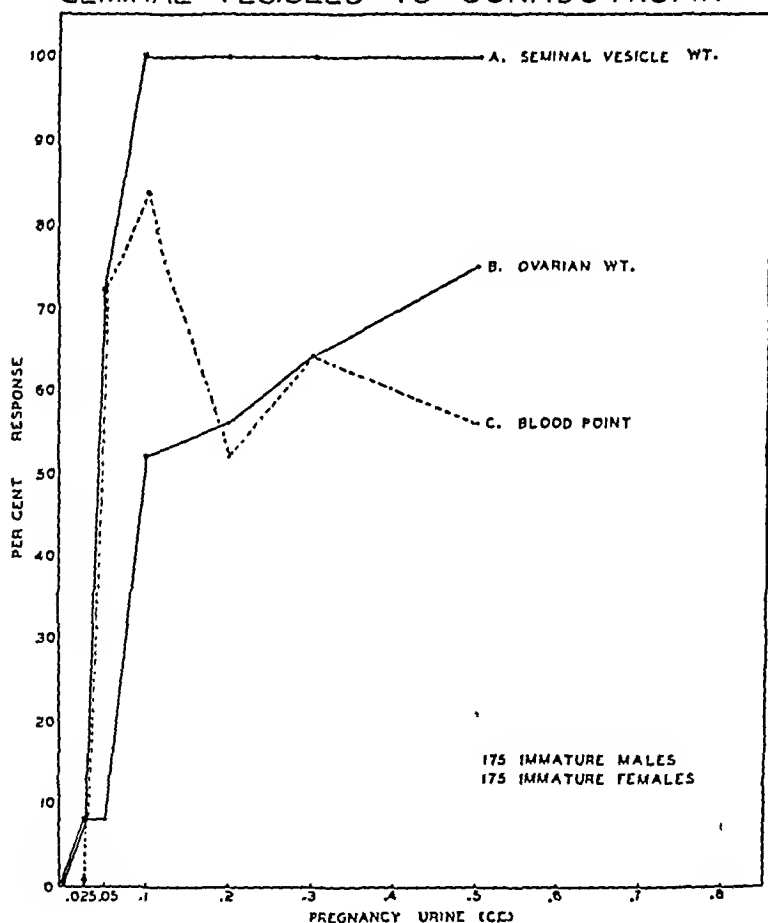


Fig. 1.

gonadotropin has been shown by Deansley,³⁰ Korenehevsky, Dennison, and Simpson,³¹ D'Amour and D'Amour,³³ Bischoff³² and Sealey and Sondern.²⁹ It also meets the requirements of the League of Nations Health Organizations³⁴ for comparison of the International Standard of chorionic gonadotropin.

A study was made of the effect of the variation in the spread of the injection and the results are in agreement with other workers. Two groups of 20 litter mate male rats (twenty-one days old) were injected simultaneously with extracts of pregnancy urine (0.02 c.e. total dose). Group 1 received 1 injection subcutaneously daily for three days, and Group 2 received 2 injections daily for three days. Both groups were sacrificed at ninety-six hours, and the amount of hormone determined by the assay curve. Group 1 gave 50 per cent positive responses, and Group 2, 65 per cent, corresponding, respectively, to 50 R.U. and 60 R.U. c.e. Thus in this experiment the value when only three injections were given was 16.7 per cent below that when six injections were given.

For assay purposes a dose-effect curve was constructed from a composite specimen of pregnancy urine. Rats from 47 litters of twenty-one-day-old rats were used. In general one litter mate was placed on each of two or three different dosages and one saved for a control. The positive response was taken as the weight exceeding the mean by twice the standard deviation of the control group of 30 rats. There were 20 rats at 0.025, 38 each at 0.05, 0.0625, and 0.075 c.e., 14 at 0.1 c.e., and 12 at

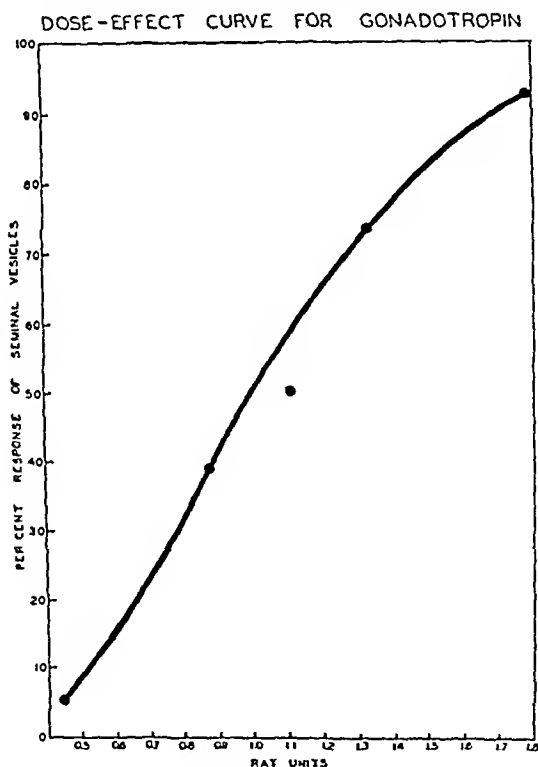


Fig. 2.

0.15 c.e. total dose of pregnancy urine; percentages of positive responses were 5, 39.5, 50.0, 73.7, 93.0, and 100, respectively. The dose giving a 50 per cent response on the curve was considered as equivalent to 1 R.U. and the dose-effect curve constructed in terms of rat units (Fig. 2).

In assaying by this method, a preliminary test was made on 4 to 10 rats in order to determine the region of the 50 per cent response. At this dose level, 15 to 25, strictly 21-day-old, male rats were injected with the same dose. This was done using rats from as many different litters as possible and injecting on different days. Litter mates from the same

litters were reserved for a control group. The percentage of responses in which the seminal vesicle weight exceeded twice the standard deviation of the mean of the control group was determined. Using the assay curve in Fig. 2, the amount of hormone in the dose tested was determined and from this the excretion per twenty-four hours calculated. The control group was compiled monthly. This obviated possible error due to seasonal variation in organ weights.

Such a method was found to be simple and to give reproducible results and offers the possibility of extrapolating dosage and minimizing the error due to biologic variation, as we have cited previously.³⁵ The accuracy of the method is illustrated in Table I. In 10 assays in which there were more than 10 rats in the assay group, seven of 10 agreed within 90 per cent or better. The effect of the number in the group upon the accuracy of the assay was shown by taking 14 assays, each with 20 animals in the group, and subdividing them into smaller groups and comparing the resulting values. For example, the group of 20 tests was compared with the first 15 tests, and with the first and second groups of 10 and the two groups of 10 with each other. The results are shown in Table II. If only the first 15 rats had been used in the assay, 12 of the 14 assays would have had an agreement of 90 per cent or better, 9 of 14, 95 per cent or better, and all within 85 per cent. Had either the first group or second group of 10 been used only seven of 14 would have agreed within 90 per cent. Only one of 14 of the two groups of 10 each agreed within 90 per cent. From this it was decided to assay using 15 to 25 rats for each assay.

TABLE I. QUANTITATIVE ASSAY OF GONADOTROPIN

NUMBER	TOTAL DOSE PREG. URINE (C.G.)	NO. MALES	PER CENT POSITIVE	RAT UNITS		PER CENT AGREEMENT
				PER DOSE	PER C.C.	
26-1	0.010	12	25.0	0.74	74.0	93
	0.015	20	65.0	1.20	80.0	
26-2	0.02	16	25.0	0.74	37.0	90
	0.03	16	50.0	1.00	33.3	
26-3	0.015	20	30.0	0.79	52.7	95 91, 97
	0.200	20	50.0	1.00	50.0	
	0.030	20	80.0	1.45	48.3	
26-6	0.02	15	53.3	1.04	52.0	87
	0.02	20	65.0	1.20	60.0	
26-7	0.015	20	25.0	0.74	49.3	91
	0.020	16	56.3	1.08	54.0	
30-1	0.03	23	34.8	0.84	28.0	82
	0.04	16	75.0	1.36	34.0	
30-2	0.03	20	55.0	1.06	35.3	94
	0.03	16	50.0	1.00	33.3	
35-1	0.20	19	42.1	0.91	4.6	91
	0.30	13	69.2	1.26	4.2	
36-2	0.04	16	75.0	1.36	34.0	86
	0.05	16	81.3	1.47	29.4	
47-1	0.15	16	37.5	0.87	5.8	92
	0.20	16	68.8	1.25	6.3	

Part II. Excretion of Estrogens and Gonadotropins in Normal Pregnancy and in Toxemias of Pregnancy

The estrogen and gonadotropin excretion has been studied in 57 cases during late pregnancy (average 35 weeks) and a statistical study of the comparison of the excretion in normal pregnancy and toxemias has been made.

TABLE II. EFFECT OF NUMBER OF TEST ANIMALS ON ACCURACY OF QUANTITATIVE ASSAY OF GONADOTROPIN

P.U. NUMBER	TOTAL DOSE P.U. (C.C.)	NO. MALES	PER CENT POSITIVE	RAT UNITS		PER CENT AGREEMENT BETWEEN GROUPS			
				PER DOSE	PER C.C.	20:15	20:10	20:10	10:10
15-1	0.05	20	75.0	1.36	27.2	98	83	81	67
		15	73.3	1.33	26.6				
		10	60.0	1.13	22.6				
		10	90.0	1.68	33.6				
26-1	0.015	20	65.0	1.20	80.0	98	94	95	89
		15	66.7	1.22	81.3				
		10	60.0	1.13	75.3				
		10	70.0	1.27	84.6				
26-3	0.015	20	30.0	0.79	52.7	85	85	89	75
		15	20.0	0.67	44.7				
		10	20.0	0.67	44.7				
		10	40.0	0.89	59.3				
26-3	0.02	20	50.0	1.00	50.0	96	79	79	62
		15	46.7	0.96	48.0				
		10	30.0	0.79	39.5				
		10	70.0	1.27	63.5				
26-3	0.03	20	80.0	1.45	48.3	92	88	100	88
		15	73.3	1.33	44.3				
		10	70.0	1.27	42.3				
		10	80.0	1.45	48.3				
26-6	0.02	20	65.0	1.20	60.0	98	83	83	69
		15	66.7	1.22	61.0				
		10	50.0	1.00	50.0				
		10	80.0	1.45	72.5				
26-7	0.015	20	25.0	0.74	49.3	97	94	91	85
		15	26.7	0.76	50.7				
		10	30.0	0.79	52.7				
		10	20.0	0.67	44.7				
27-2	0.16	20	60.0	1.13	7.1	93	100	100	100
		15	66.7	1.22	7.6				
		10	60.0	1.13	7.1				
		10	60.0	1.13	7.1				
29-1	0.2	20	60.0	1.13	5.7	100	79	78	62
		15	60.0	1.13	5.7				
		10	40.0	0.89	4.5				
		10	80.0	1.45	7.3				
29-2	0.2	20	75.0	1.36	6.8	100	94	93	88
		15	75.0	1.36	6.8				
		10	70.0	1.27	6.4				
		10	80.0	1.45	7.3				
32-1	0.2	20	75.0	1.36	6.8	99	93	84	78
		15	73.3	1.33	6.7				
		10	80.0	1.45	7.3				
		10	60.0	1.13	5.7				
32-2	0.1	20	45.0	0.94	9.4	98	83	84	70
		15	46.7	0.96	9.6				
		10	60.0	1.13	11.3				
		10	30.0	0.79	7.9				
43-1	0.02	20	85.0	1.55	77.5	87	92	94	86
		15	93.3	1.78	89.0				
		10	90.0	1.68	84.0				
		10	80.0	1.45	72.5				
52-1	0.02	20	45.0	0.94	47.0	90	95	94	89
		15	53.3	1.04	52.0				
		10	40.0	0.89	44.5				
		10	50.0	1.00	50.0				

In this study, 43 cases had determinations of both estrogens and gonadotropins and 14 had only estrogen determinations. Whenever possible two consecutive twenty-four-hour specimens were obtained. In general each specimen was assayed separately but occasionally the two specimens were pooled before assay. Two extracts were made for each specimen and 20 rats were used for each pharmacologic assay. Thus a two-day assay value for estrogen is the result of the use of approximately 90 rats. It was not always possible to determine gonadotropin on both specimens. When both assays were made on both specimens the values used in the statistical study were the averages of the two days; when gonadotropin was not determined on the second specimen the estrogen determination on the second day was omitted. This procedure was followed because of its bearing on the estrogen-gonadotropin ratio discussed later. The twenty-four-hour urine volumes were calculated for the eclamptic patients. The unabridged data are shown in Table III.

1. CLASSIFICATION

Group A.—This group corresponds to the group A of the classification of the American Committee on Maternal Welfare¹⁶ and consists of 14 patients with hypertensive and renal disease in whom the disease was not peculiar to pregnancy but aggravated by it. It was not subdivided into Group I and II. Table IV. The week of pregnancy ranged from 31 to 40 (average, 35.1 weeks).

Group B.—This group corresponds to Group B of the classification of the American Committee and consists of toxemic patients in whom the disease was dependent upon pregnancy or peculiar to it. Group BI consists of 13 pre-eclamptic patients; the week of pregnancy ranged from 29 to 38 (average 34.3 weeks), and Group BII of five eclamptic patients ranging from twenty-nine to forty-four weeks of pregnancy (average 38.2 weeks) (Table IV).

Group C.—This group consists of 11 patients hospitalized pending cesarean section or because of mild cardiac disease. This group was used as a control group (Table IV). This group ranged from twenty-eight to forty weeks of pregnancy (average, 34.9 weeks).

2. EXCRETION OF ESTROGEN

The excretion of estrogen varied greatly in each group of patients. Although there was in general a low excretion in the pre-eclamptic and eclamptic patients, the overlapping of values made it difficult, unless a value was extreme, definitely to assign it to any group (Fig. 3). The excretion per cubic centimeter is found in Tables III and IV. The twenty-four-hour excretion values expressed in I.U. per twenty-four hours range from 15,150 to 65,150 in the normal group (Group C), from 6,850 to 78,400 in the hypertensive and renal disease group (Group A), from 2,500 to 34,350 in the pre-eclamptic group (Group BI), and from 5,000 to 22,800 in the eclamptic group (Group BII) (Table IV, Figs. 3, 4, and 5). The estrogen excretion, I.U. per twenty-four hours, in the various groups expressed as the mean \pm S.E. was as follows: Normal group, 38,260 \pm 5,240; hypertensive and renal disease group, 37,540 \pm 5,770; pre-eclamptic group, 17,620 \pm 3,030; eclamptic group, 11,800 \pm 3,670. The lowered excretion of estrogen in pre-eclampsia and eclampsia is in agreement with most investigators. However, no attempt can be made to compare the quantitative values of various workers^{1-13, 15, 36-54, 64, 65} because of the different methods of assay and also of extractions employed in different laboratories.

Since any extreme value may greatly effect a mean value, it seemed advisable to subject these data to statistical analysis in order to determine the significances of the differences observed in the excretion in the various groups. Fisher's method⁵⁵ of testing the significance between two means was used. The difference between the estrogen excretion in the normal and the hypertensive and renal disease groups was not significant ($P = > 0.9$), but the differences observed between the normal and the pre-eclamptic or combined pre-eclamptic and eclamptic, the normal and eclamptic, and the pre-eclamptic and hypertensive renal disease groups were significant ($P = < 0.01$). There is less than one chance per 100 that differences such as observed between the normal and the pre-eclamptic group could have been obtained by chance from another group

ESTROGEN AND GONADOTROPIN IN LATE PREGNANCY

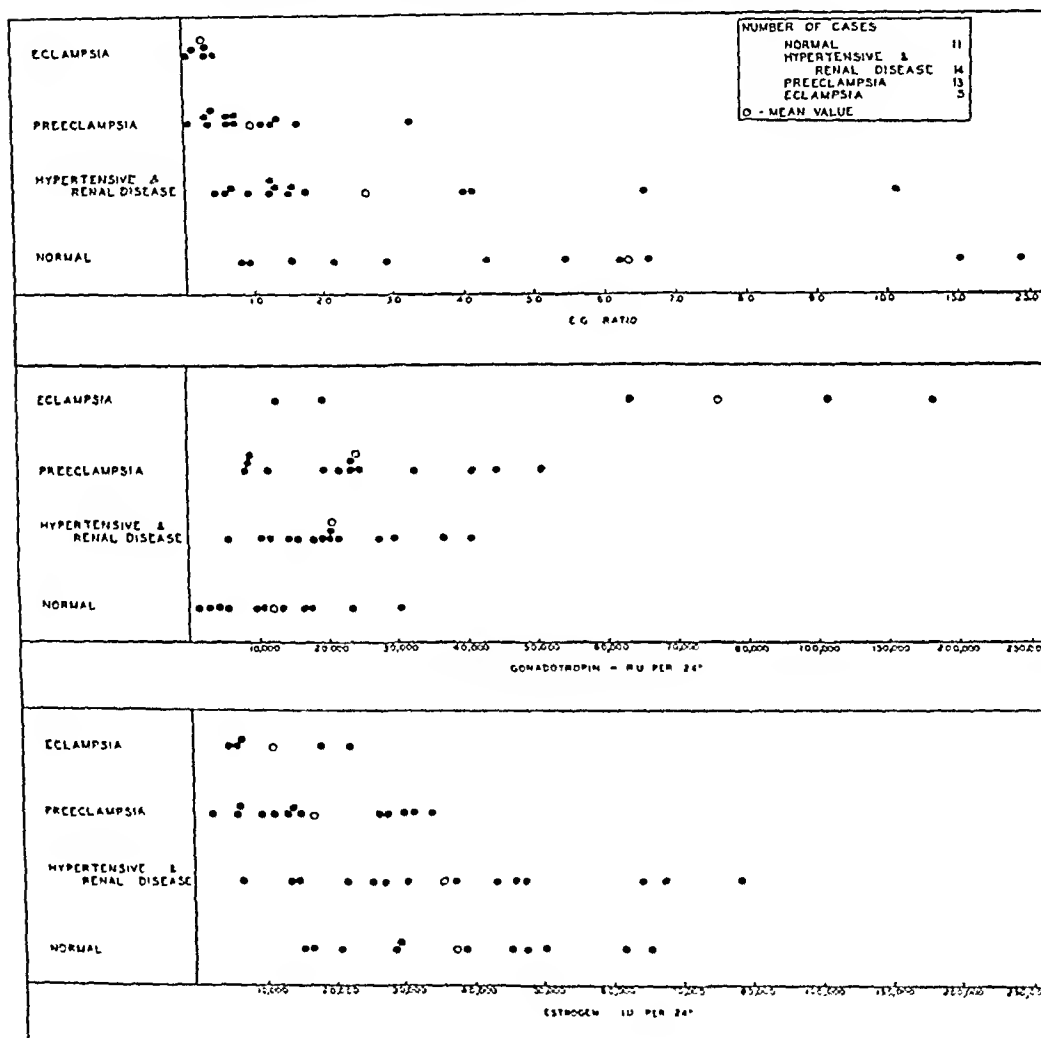


FIG. 3.

of "normal" patients and also that there was less than one chance per 200 that a mean as low as that found in the pre-eclamptic could have been obtained by chance in another group of "normal" patients. There was a significant difference between the estrogen excretion in the pre-eclamptic and hypertensive and renal disease groups ($P = < 0.01$).

TABLE III. EXCRETION OF ESTROGENS AND GONADOTROPINS IN LATE PREGNANCY

SPEC. NO.	WK. PREG.	24° VOL- UME	ESTROGENS†				GONADOTROPINS			E:G RATIO
			NO. PREP- ARA- TIONS	NO. RATS	I.U. PER C.C.	I.U. PER 24°	NO. RATS	I.U. PER C.C.	I.U. PER 24°	
Group A. Hypertensive and Renal Disease										
25-1	37	1285	2	40	61.0	78,400	26	15.2	19,500	4.01
30-1	33	1300	3	60	37.6	48,800	39	30.6	39,800	1.23
30-2		985	2	39	44.6	43,900	70	33.8	33,300	1.32
32-1	31	2075	2	40	27.9	83,000	21	6.1	18,700	4.57
32-2		1385	2	45	33.4	46,300	20	9.4	13,000	3.55
37-1	37	1805	2	40	25.6	46,200	24	1.7	3,100	14.77
37-2		1955	2	40	24.5	47,900	20	3.8	7,400	6.50
39-1	39	1200	2	40	21.4	25,700	14	26.0	31,200	0.82
39-2		1350	3	59	21.6	29,200	19	20.6	27,800	1.05
53-(1 & 2)*	37	2335	3	58	18.6	43,400	18	11.8	27,400	1.58
55-(1 & 2)	31	600	2	40	23.1	13,900	19	33.4	20,000	0.69
56-(1 & 2)	34	475	2	40	30.3	14,400	20	23.5	11,300	1.29
63-1	34	715	2	26	4.0	2,900	18	13.1	9,400	0.31
63-2		1590	3	41	6.8	10,800	20	12.0	19,100	0.57
65-1	34	1960	2	40	26.2	51,400	18	11.0	21,600	2.38
65-2		930	3	60	25.6	23,800	18	23.0	21,400	1.11
78-1	40	2075	2	40	11.7	24,300	19	22.3	46,400	0.52
78-2		1985	2	40	13.5	26,800	20	17.7	35,100	0.76
82-1	37	1510	2	42	16.2	24,500	20	9.4	14,200	1.72
82-2		1460	2	43	13.3	19,400	16	14.4	21,000	0.92
83-1	32	1930	2	40	16.7	32,200	17	10.9	21,000	1.53
83-2		2610	2	40	11.3	29,500	19	7.3	19,100	1.55
91-2	35	2460	1	20	27.3	67,200	12	4.2	10,200	6.58
91-3		1780	2	45	23.3	41,500				-
49-1	36	2135	2	40	26.0	55,500				
49-2		2965	2	40	18.6	55,100				
85-1	26	250	2	44	43.3	10,800				
85-2		1800	2	40	17.0	30,600				
90-2	35	1900	2	40	23.3	44,300				
90-3		1430	1	20	29.4	42,000				
93-1	30	1285	2	40	29.2	37,500				
93-2		1365	2	40	24.8	33,900				
93-3		2160	2	40	18.8	23,700				
97-1	34	670	2	40	12.2	8,200				
Group BI. Pre-Eclampsia										
35-1	30	1900	4	58	3.2	6,100	32	4.4	8,300	0.73
35-2		1900	2	35	4.2	8,000				
35-3		2030	2	33	3.6	7,300				
35-4		2480	2	34	4.1	10,200				
36-1	37	855	2	40	42.7	36,500	19	26.8	22,000	1.59
36-2		815	2	40	22.9	18,700	32	31.7	25,800	0.72

*Parentheses denote that specimens were pooled before assay.

†Estrogen values are expressed in equivalents of crystalline estrone.

TABLE III—CONT'D

SPEC. NO.	WK. PREG.	24° VOL- UME	ESTROGENS†				GONADOTROPINS			E:G RATIO
			NO. PREP- ARA- TIONS	NO. RATS	I.U. PER C.C.	I.U. PER 24°	NO. RATS	R.U. PER C.C.	R.U. PER 24°	
40-1	35	670	2	40	46.6	31,200	15	34.7	23,200	1.35
40-2		1055	2	40	39.3	41,500				
41-1	29	685	2	40	9.6	6,600	15	12.8	8,800	0.75
41-2		1070	2	40	10.9	11,700				
41-3		1030	2	40	10.9	11,000				
46-1	36	1600	2	40	9.0	14,400	18	7.0	11,300	1.28
64-1	33	1090	2	40	24.1	26,300	19	7.8	8,500	3.09
64-2		1485	2	45	18.6	27,600	16	5.4	8,000	3.44
66-1	29	1530	3	45	7.3	11,200	17	21.3	29,600	0.34
66-2		1660	2	40	7.1	11,800	18	21.8	36,200	0.33
67-1	31	1515	2	40	6.2	9,400	18	10.1	15,300	0.61
67-2		2450	3	60	8.2	20,100	23	12.7	31,100	0.65
72-1	38	925	2	40	38.0	35,200	20	19.2	17,800	1.98
72-2		720	2	40	34.9	25,100	21	28.2	20,300	1.24
77-1	36	2100	2	40	8.6	18,100	11	21.2	44,500	0.41
77-2		4250	2	39	11.9	50,600	20	13.3	56,500	0.89
89-2	36	575	3	45	4.3	2,500	20	77.5	44,600	0.06
89-3		800	4	46	4.2	3,400				
94-1	38	685	3	50	19.7	13,500	19	61.2	41,900	0.32
94-2		800	2	40	7.5	6,000				
101-1	38	550	2	40	17.3	9,500	10	39.5	21,700	0.44
101-2		1300	2	40	17.0	22,100				
86-1	37	1120	2	45	12.8	14,300				
86-2		2205	2	40	13.5	29,800				
92-1	42	1090	3	56	4.5	4,900				
100-1	35	1300	1	20	6.3	8,200				
100-2		2000	2	40	5.9	11,800				
102-1	40	1800	2	40	15.3	27,500				
102-2		3600	2	40	11.0	39,600				
103-1	37	1900	2	40	17.8	33,700				
103-2		3200	2	40	13.1	41,800				
104-1	35	800	2	40	14.0	11,200				
104-2		1650	2	40	13.1	21,600				
106-1	35	1070	1	33	2.1	3,500				
106-2		2265	1	13	2.7	4,800				

Group BII. Eclampsia

42-1	44	2900	2	40	7.9	22,800	14	21.8	63,200	0.36
43-1	40	2340	4	48	2.1	5,000	20	77.5	181,400	0.03
47-1	43	2120	4	37	2.8	6,000	32	6.0	12,800	0.47
80-1	29	1560	2	37	11.9	18,400	17	69.0	107,600	0.17
96-1	35	1060	2	45	6.4	6,800	17	18.3	19,300	0.35

*Twenty-four-hour volumes calculated.

†See footnote at beginning of table.

TABLE III—CONT'D

SPEC. NO.	WK. PREG.	24° VOL- UME	ESTROGENS†				GONADOTROPINS			E:G RATIO
			NO. PREP- ARA- TIONS	NO. RATS	I.U. PER C.C.	I.U. PER 24°	NO. RATS	R.U. PER C.C.	R.U. PER 24°	
Group C. Normals										
27-1	37	870	2	45	72.5	63,100	39	4.2	3,600	17.34
27-2		650	3	75	93.4	60,700	20	7.1	4,600	13.23
29-1	34	1450	2	45	40.1	58,100	20	5.7	8,200	7.10
29-2		1695	2	45	42.6	72,200	20	6.8	11,500	6.26
33-1	35	2960	3	75	19.4	57,400	22	10.0	29,600	1.94
33-2		2370	2	40	18.0	42,700	18	7.7	18,200	2.34
44-1	31	3645	3	59	10.7	39,000	19	0.5	1,600	23.78
44-2		3660	2	41	14.7	53,800				
59-(1 & 2)	28	935	2	45	18.1	16,900	21	2.9	2,700	6.24
61-(1 & 2)	39	500	2	40	41.6	20,800	11	26.5	13,300	1.57
62-(1 & 2)	40	370	3	60	80.4	29,700	20	14.8	5,500	5.43
69-1	40	2270	2	40	21.2	48,100	20	6.8	15,400	3.12
69-2		2460	2	40	19.3	47,500	20	7.2	17,700	2.68
73-1	40	665	3	65	32.1	21,300	20	37.7	25,100	0.85
73-2		1150	2	40	31.9	36,700	16	31.0	35,700	1.03
79-1	29	1605	2	50	10.7	17,200	23	11.1	17,800	0.96
79-2		910	2	40	14.3	13,000	20	18.8	17,100	0.76
81-1	31	435	2	40	75.5	32,800	16	21.6	9,400	3.50
81-2		850	3	65	68.4	58,100	15	13.3	11,300	5.14
98-1	39	775	2	40	39.2	29,300				
98-2		950	2	40	31.3	29,700				
107-1	38	2235	2	40	9.5	21,000				
107-2		865	2	40	15.8	13,700				
107-3		4470	2	40	4.8	21,900				
Group D. Miscellaneous†										
87-1	40	1630	2	40	85.4	139,200	12	17.3	28,200	4.94
87-2		760	2	70	81.6	62,000				
71	39	675	2	40	63.7	43,000	18	22.8	15,400	2.79
28	36	2700	2	40	48.0	129,600	10	8.9	24,000	5.39
88	39	340	1	20	25.7	8,700				
22	14	820	2	50	13.6	11,200	20	68.0	55,800	
50	31	333	2	52	32.0	10,700	31	15.2	50,600	0.21
76	30	1515	2	38	5.0	7,600	20	2.7	4,000	1.89
105-1	37	850	2	40	32.7	26,800				
105-2		1400	2	40	31.0	43,400				
105-3		550	2	40	33.8	18,600				

†Classification of cases: Cases 22 and 50 hyperemesis gravidarum; Case 23 diabetes mellitus; Cases 28 and 88 epilepsy; Case 35 abruptio placentae; Cases 45, 54, 58 hypertensive and renal disease; Case 51 diabetes insipidus; Case 71 edema; Case 75 hysteria, polyhydramnios, partial separation of placenta; Case 76 death of fetus; Case 87 mild pre-eclampsia; Case 95 achondroplastic dwarfism; Case 105 placenta previa; Case 108 pseudomucinous cystadenoma of the ovary.

TABLE III—CONT'D

SPEC. NO.	WK. PREG.	24° VOL-UME	ESTROGENS†				GONADOTROPINS			E:G RATIO
			NO. PREP-ARA-TIONS	NO. RATS	I.U. PER C.C.	I.U. PER 24°	NO. RATS	R.U. PER C.C.	R.U. PER 24°	
35-(8&9)**	32	2780	2	42	3.6	10,000				
75-1	37	4520	2	42	19.5	88,100	20	9.5	41,800	2.11
75-2		4790	3	85	20.7	99,200	20	6.0	28,700	3.45
95-1	38	2150	2	42	15.9	34,200				
95-2		1430	2	40	22.6	32,300	14	23.0	32,900	0.98
95-3		2670	2	40	20.5	54,700				
23-1	37	800	2	40	141.5	113,200	15	48.8	39,000	2.90
51-1	37	6700	2	39	9.5	63,700				
51-2		5480	1	20	9.6	52,600				
51-(6&7)**		6025	3	60	16.4	98,800	18	0.8	4,600	21.58
108-1	31	710	2	40	13.5	9,600				
108-2		530	2	40	19.7	9,400				
108-3		1690	2	40	9.1	15,400				
45-1	23	2170	2	22	1.1	2,400				
45-2		3530	1	9	1.2	3,500				
54-(1&2)**	24	790	2	40	12.0	9,500	20	5.9	4,700	
58	10	1620	2	35	3.4	5,500	22	16.3	26,400	

** (1 & 2) denotes average of 2 specimens. (6 & 7) (8 & 9) denotes pooled specimens.

3. EXCRETION OF GONADOTROPIN

The excretion of gonadotropin was determined on the same groups of patients described above (Table IV). In each group the variation was great and values in each group overlapped those of other groups. (Fig. 3). The concentration per cubic centimeter is found in Tables III and IV. The range of the gonadotropin values varied in the normal group (Group C) from 1,600 to 30,400, in the hypertensive and renal disease group (Group A), from 5,250 to 40,750, in the pre-eclamptic group (Group BI), from 8,250 to 50,500, and in the eclamptic group (Group BII) from 12,800 to 181,400 R.U. per twenty-four hours (Table IV). The mean values (Mean \pm S.E.) for these groups were: normal group, $12,340 \pm 2,760$; hypertensive and renal disease group, $20,690 \pm 2,660$; pre-eclamptic group, $24,470 \pm 3,960$; eclamptic group, $76,860 \pm 31,210$ R.U. per twenty-four hours. Comparison of these means by the Fisher method⁵⁵ showed a significant difference between the excretion of gonadotropin in the normal and pre-eclamptic groups ($P = 0.03$), the normal and the eclamptic groups ($P = < 0.01$), the normal and combined pre-eclamptic and eclamptic groups ($P = < 0.06$), the normal and the hypertensive and renal disease groups ($P = 0.04$), but no difference between the pre-eclamptic and hypertensive and renal disease group ($P = 0.43$). Because of lack of uniformity of standards in various laboratories no attempt can be made to compare these values with those of other workers.^{1-3, 5, 8, 15, 36, 37, 39, 45, 52, 56-63}

4. ESTROGEN-GONADOTROPIN RATIO

The individual variation in the excretion of either estrogen or gonadotropin is extreme and the standard deviation in any group may be larger than an individual value in the group. In general, it seemed that

in individual cases there was a relationship between the amount of estrogen and gonadotropin excreted, i.e., when the estrogen was high the gonadotropin also tended to be high (Fig. 4). This observation led to the calculation of the estrogen-gonadotropin ratio which is an arbitrary value dependent upon the units chosen to express both estrogen and gonadotropin. These E:G ratios (estrogen to gonadotropin ratio) ranged as follows: normal group (Group C), 0.86 to 23.78; hypertensive and renal disease group (Group A), 0.44 to 10.64; pre-eclamptic group (Group BI), 0.06 to 3.27; and the eclamptic group (Group BII), 0.03 to 0.47. The mean E:G ratio values (Mean \pm S. E.) for the various groups were: normal, 6.38 ± 2.13 ; hypertensive and renal disease, 2.63 ± 0.77 ; pre-eclamptic, 0.97 ± 0.23 ; eclamptic, 0.28 ± 0.08 . Considered statistically, there was a significant difference between the means of the normal and the pre-eclamptic groups ($P = 0.01$) but the mean of the hypertensive and renal disease group fell between these two groups and showed only a borderline significance to each group ($P = 0.07$ and $P = 0.06$, respectively). That is, there were approximately 3 chances per hundred that a mean ratio of another group of similar patients would fall within the range of the normal group or that of the

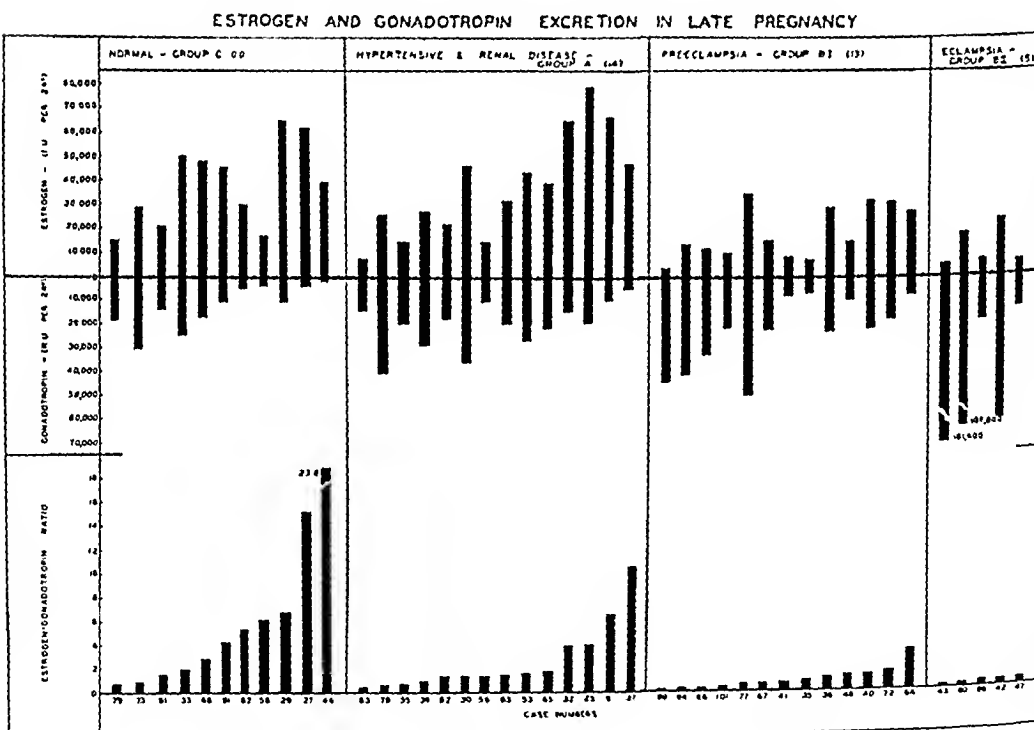


Fig. 4.

pre-eclamptic group. Comparison by the Fisher method of the normal and the eclamptic groups showed no significant difference ($P = 0.08$) between the means probably due to the small number in the eclamptic group (5) and the extreme range in values in the normal group. If the two extremely high ratios (which varied by more than twice the standard deviation of the mean) are omitted, which lowers the mean, and the difference between these means, the difference becomes significant ($P = < 0.01$). When the pre-eclamptic and eclamptic groups are com-

bined there is a significant difference ($P = < 0.01$) between this mean (0.78 ± 0.56) and that of the normal or of the hypertensive and renal disease group. It seems that the E:G ratio is a better index of hormone values in individual cases than the twenty-four-hour excretion value of either estrogen or gonadotropin. In the normal group, 9 of 11 ratios, and in the pre-eclamptic group only 2 of 13 were above 1.5. Furthermore, this value is independent of the twenty-four-hour urine volume and the accuracy of its collection. (Figs. 3, 4, 5.)

5. FURTHER OBSERVATIONS ON EXCRETION OF ESTROGEN

Since it was not possible to do gonadotropin determinations on all patients and sometimes only on one specimen, the data on estrogen excretion are more complete. The data in this group represent the complete data on the twenty-four-hour estrogen excretion and consist of the 43

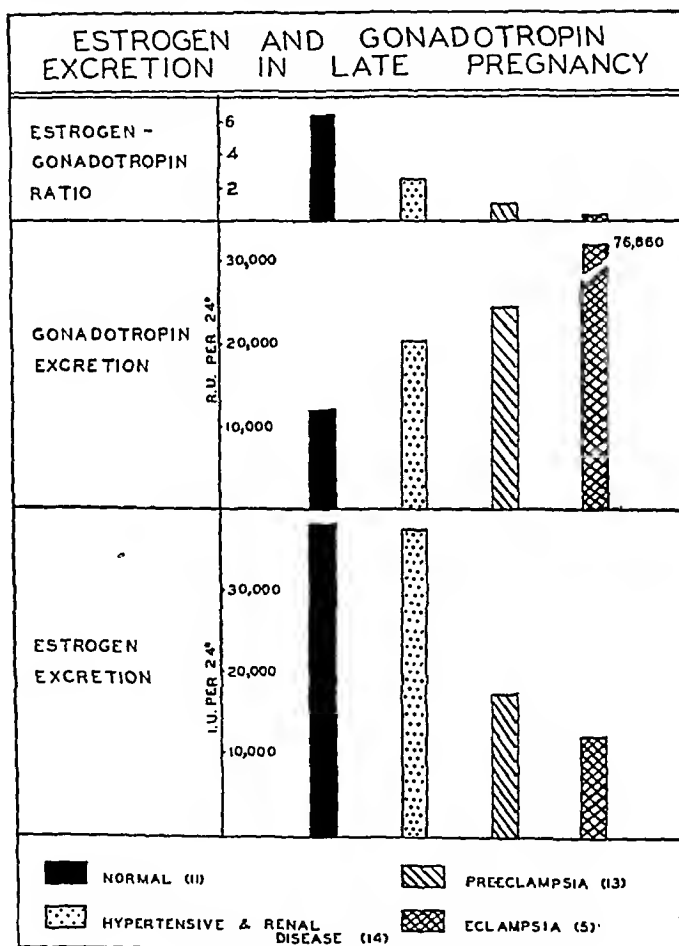


Fig. 5.

cases in groups discussed above and 14 other cases in which only estrogen was determined. In 32 cases the estrogen value was determined by averaging the assays of two consecutive specimens, in six cases pooled specimens and nine cases the value of only one specimen. Excluding the trial assay these values are based on approximately 3,000 tests. The twenty-four-hour excretion values varied in the normal group (13 cases)

TABLE IV. EXCRETION OF HORMONES IN LATE PREGNANCY

SPEC. NO.	ESTROGEN† I.U. PER C.C.	ESTROGEN† I.U. PER 24 HOURS	GONADOTROPIN R.U. PER C.C.	GONADOTROPIN† R.U. PER 24 HOURS	E:G RATIO	24° VOLUME
<i>Group A. Hypertension and Renal Disease</i>						
25-1	61.0	78,400	15.2	19,500	4.01	1,285
30-1 & 2	41.1	46,350	32.2	36,350	1.28	1,143
32-1 & 2	30.7	64,650	7.8	15,850	4.06	2,180
37-1 & 2	25.1	47,050	2.8	5,250	10.64	1,880
39-1 & 2	21.5	27,450	23.3	29,500	0.94	1,275
53-(1 & 2)	18.6	43,400	11.8	27,400	1.58	2,335
55-(1 & 2)	23.1	13,900	33.4	20,000	0.69	600
56-(1 & 2)	30.3	14,400	23.5	11,300	1.29	475
63-1 & 2	5.4	6,850	12.6	14,250	0.44	1,153
65-1 & 2	25.9	37,600	17.0	21,500	1.75	1,445
78-1 & 2	12.6	25,550	20.0	40,750	0.64	2,030
82-1 & 2	14.8	21,950	11.9	17,600	1.32	1,485
83-1 & 2	14.0	30,850	9.1	20,050	1.54	2,270
91-2	27.3	67,200	4.2	10,200	6.58	2,460
N = 14						
Mean ± S. E.	25.10 ± 3.66	37,540 ± 5770	16.06 ± 2.53	20,690 ± 2,660	2.63 ± 0.77	1,573 ± 169
<i>Group B1. Pre-eclampsia</i>						
35-1	3.2	61,100	4.4	8,300	0.73	1,900
36-1 & 2	32.8	27,600	29.3	24,350	1.16	835
40-1	46.6	31,200	34.7	23,200	1.35	670
41-1	9.6	6,600	12.8	8,300	0.75	685
46-1	9.0	14,400	7.0	11,300	1.28	1,600
64-1 & 2	21.4	26,950	6.6	8,250	3.27	1,288
66-1 & 2	7.2	11,500	21.6	32,900	0.34	1,595
67-1 & 2	7.2	14,750	11.4	23,200	0.63	1,983
72-1 & 2	36.5	30,150	23.7	19,050	1.61	823
77-1 & 2	10.3	34,350	17.3	50,500	0.65	3,175
89-1	4.3	2,500	77.5	44,600	0.06	575
94-1	19.7	13,500	61.2	41,900	0.32	685
101-1	17.3	9,500	39.5	21,700	0.44	550
N = 13						
Mean ± S. E.	17.32 ± 3.74	17,620 ± 3,030	26.69 ± 6.12	24,470 ± 3,960	0.97 ± 0.23	1,259 ± 215

Group BII. Eclampsia						
42-1	7.9	22,800	21.8	63,200*	0.36	2,900
43-1	2.1	5,000	77.5	181,400	0.03	2,340
47-1	2.8	6,000	6.0	12,800	0.47	2,130
80-1	11.9	18,400	69.0	107,600	0.17	1,560
96-1	6.4	6,800	18.3	19,300	0.35	1,060
N = 5						
Mean \pm S. E.	6.22 \pm 1.79	11,900 \pm 3,670	38.52 \pm 14.48	76,860 \pm 31,210	0.28 \pm 0.08	1,998 \pm 318
Group C. Normals						
27-1 & 2	83.0	61,900	5.6	4,100	15.29	760
29-1 & 2	41.4	65,150	6.2	9,850	6.68	1,573
33-1 & 2	18.7	50,050	8.9	23,900	2.14	2,665
44-1	10.7	39,000	0.5	1,800	23.78	3,645
59-(1 & 2)	18.1	16,900	2.9	2,700	6.24	935
61-(1 & 2)	41.6	20,800	26.5	13,300	1.57	500
62-(1 & 2)	80.4	29,700	14.8	5,500	5.43	370
69-1 & 2	20.3	47,800	7.0	16,550	2.90	2,365
73-1 & 2	32.0	29,000	34.4	30,400	0.94	908
79-1 & 2	12.5	15,150	15.0	17,450	0.86	1,258
81-1 & 2	72.0	45,450	17.5	10,350	4.32	643
N = 11						
Mean \pm S. E.	39.15 \pm 8.26	38,260 \pm 5,240	12.66 \pm 3.13	12,340 \pm 2,760	6.38 \pm 2.13	1,420 \pm 315

*Parentheses indicate that specimens were pooled before assay, 1 and 2 indicates average of 2 specimens.

†Estrogen values are expressed in equivalents of crystalline estrone.

‡Twenty-four-hour volume calculated.

from 15,150 to 65,150 I.U., in the hypertensive and renal disease group (19 cases) from 6,850 to 78,400, in the pre-eclamptic group (20 cases) from 2,950 to 37,850 I.U. and the eclamptic group (5 cases) 5,000 to 22,800 I.U. per twenty-four hours. The mean excretion values mean \pm S.E. (I.U. per 24^o), of the different groups were: normal, $36,550 \pm 4,780$; hypertensive and renal disease, $35,580 \pm 4,490$; pre-eclamptic, $18,490 \pm 2,600$; eclamptic, $11,800 \pm 3,670$. These differences, considered statistically,⁵⁵ show a significant difference between the estrogen excreted by the normal group and the pre-eclamptic group ($P = < 0.01$), and between the pre-eclamptic and hypertensive and renal disease groups ($P = < 0.01$), but not between the normal and the hypertensive and renal disease group ($P = 0.87$).

General inspection of the data on the excretion of estrogens on two consecutive days suggested that there was a tendency toward larger estrogen value in the larger twenty-four-hour volume. These data were arranged in two groups according to the smaller and larger volumes. In normal patients the group with smaller volumes excreted $35,870 \pm 5,370$ I.U. per twenty-four hours and with the large volumes the same patients excreted $45,670 \pm 5,890$ I.U. per twenty-four hours. This difference was not statistically significant ($P = 0.23$). Similarly in the hypertensive and renal disease group the excretion by the smaller volume group was $31,480 \pm 4,020$ I.U. and by the larger, $41,720 \pm 5,100$ I.U. per twenty-four hours, and the difference was not significant ($P = 0.13$). However, in the pre-eclamptic group the lower volume group excreted $15,370 \pm 2,280$ I.U. and the higher volume group $23,670 \pm 3,470$ I.U. per twenty-four hours. These differences gave a probability of 0.05, or 2.5 chances per 100 that a mean as high as that observed in the high volume group could have resulted by chance. It indicates that in pre-eclampsia there may be a kidney excretion factor for estrogens. Furthermore, in about 56 per cent of the normal patients, 43 per cent of the hypertensive and renal disease patients, and 78 per cent of the pre-eclamptic patients, the amount of estrogen in the lower of the two volumes was less than 80 per cent of that calculated on the basis of the excretion in the higher volume specimen. Such a kidney excretion factor has been suggested recently by Hain.⁴⁶

III. Excretion of Estrogen and Gonadotropin in Other Pathologic Conditions of Pregnancy

Estrogen and gonadotropin excretion during pregnancy was determined in 17 additional cases not included in the above series; 4 cases were studied early in pregnancy and 13 cases presented a variety of different conditions. These data are found in Table III. The four cases of toxemia observed too early in pregnancy to be included in the above studies are reported merely for the benefit of other workers. In the other conditions complicating pregnancy no attempt has been made to evaluate the findings in respect to reports in the literature. In this group the ratios were high in patients without toxic symptoms except for the dwarf. Although it is unwise and difficult to evaluate individual cases a few suggestions follow:

In the mild pre-eclamptic (Case 87), both the estrogen and gonadotropin values were high and the E:G ratio was normal. There was one patient (Case 71) who showed no symptoms other than marked edema at the time the hormone determinations were made. The estrogen and gonadotropin excretion was normal at this time, and the ratio was normal. The patient later developed pre-eclampsia.

There were two cases of epilepsy in this group. In the mild case (Case 28) the estrogen and gonadotropin were both high and the ratio high. In the other case (Case 88), only estrogen was determined and was found to be low.

Two cases of hyperemesis gravidarum were studied. One case (Case 22) was early in pregnancy; the other case (Case 50) showed low estrogen and high gonadotropin with a resulting low E:G ratio. Only one case (Case 76) was studied in which the death of the fetus was the complicating condition. Both estrogen and gonadotropin were low and the ratio was low but normal.

Estrogen was normal in the one case of placenta previa (Case 105).

One patient was studied in two pregnancies. Data on her second pregnancy were included in Group BI. Her third pregnancy was complicated with partial separation of the placenta. At this time (30 weeks) the estrogen value was 10,000 I.U. per twenty-four hours; in the previous pregnancy (32 weeks) the estrogen ranged from 7,000 to 10,000 I.U. per twenty-four hours on four consecutive days. Both infants were stillborn.

In one case (Case 75) the pregnancy was complicated by hysteria, polyhydramnios, and partial separation of the placenta. Both estrogen and gonadotropin were high but the ratio was normal.

The excretion of estrogen was normal but the gonadotropin was high in an achondroplastic dwarf (Case 95). The ratio was low.

Both estrogen and gonadotropin were high in the patient (Case 23) in whom pregnancy was complicated by diabetes mellitus and hypertension. The ratio was normal.

In a case of diabetes insipidus (Case 51), the excretion of estrogen was high and the gonadotropin was very low; the ratio was high.

Estrogen excretion was low in a patient (Case 108) with a pseudomucinous cystadenoma of the ovary.

Conclusions

When the toxemias of pregnancy are classified according to the recommendations of the American Committee on Maternal Welfare, the twenty-four-hour excretion of estrogen and gonadotropin shows certain statistically significant differences between a group of normal patients and the groups with either pre-eclampsia and eclampsia in whom the disease is considered peculiar to pregnancy or with hypertensive and renal disease which existed before pregnancy or persisted after pregnancy. Extreme individual variation of the excretion of both estrogen and gonadotropin in all groups of patients was observed as reported by other workers. The variation persisted even with pharmacologic assay of the hormones. The mean values of the different groups show a lowered excretion of estrogen in the pre-eclamptic and eclamptic group but not in the hypertensive and renal disease group and an increased excretion in gonadotropin in the pre-eclamptic, eclamptic, and hypertensive and renal disease groups. These differences are statistically significant. It is impossible to evaluate the values obtained by different investigators because of the variation in technique of extraction and quantitative assay of the estrogen and gonadotropin.

There was extreme overlapping of the values of the different groups so that it is difficult unless a value is extreme to allocate it to a specific clinical group. In general there seemed to be a relationship between the amount of estrogen and gonadotropin excreted, that is, when the estrogen value was high the gonadotropin also tended to be high. This relationship has been expressed as the estrogen to gonadotropin ratio. In the different groups the mean ratio was lowest in pre-eclamptic and eclamptic groups, somewhat higher in the hypertensive and renal disease group and highest in the normal group. There was a significant difference between the normal and pre-eclamptic groups and a borderline difference between the hypertensive and renal disease group and either the normal or the pre-eclamptic group. When the pre-eclamptic and eclamptic groups are combined there is a significant difference between the mean ratio of this group and the hypertensive and renal disease group. This ratio for individual patients is a better index of hormone relationships than the twenty-four-hour excretion of either the estrogen or the gonadotropin. In pathologic conditions of pregnancy not showing toxic symptoms this ratio is normal in general.

From this study and others, it seems that estrogens and gonadotropins are in some way definitely associated with the toxemias of pregnancy. This work was not designed to contribute to the theories of the cause of toxemias but merely to substantiate certain findings pertinent to the relationship of these hormones to the toxemias. These results indicate a lowered excretion of estrogen and an increased excretion of gonadotropin in pre-eclampsia and eclampsia. There is an increase in gonadotropin only in hypertensive and renal disease. We realize that there is great individual variation in the excretion of these hormones and have attempted to offset this variation by use of the ratio of the estrogen to the gonadotropin excretion. Furthermore, a series of determinations on one patient might give a better evaluation of the hormonal state than a comparison of these values with those of other individuals. We are aware that hormone excretion is only a part of the general problem, and that a parallel study of the blood values is desirable. The question for the future seems to be to determine the cause of these hormonal changes whether or not they are attributable to changes in the production of these hormones, to disturbance of their ratios or to altered excretory, metabolic, and storage functions of the kidneys, liver, or placenta.

Summary

The excretion of estrogen and gonadotropin has been determined in 74 cases during pregnancy; 70 cases were studied during late pregnancy (thirty-five weeks) and 4 cases in early pregnancy. Of the 70 cases studied in late pregnancy, 57 cases were used for a statistical study of the relation of these hormones to the toxemias of pregnancy. Of these, 43 cases (11 normal, 14 hypertensive and renal disease, 13 pre-eclamptic,

and 5 eclamptic patients) had parallel quantitative assays of both estrogens and gonadotropins and 14 estrogen only. The other 13 cases represented various other conditions complicating pregnancy.

In the group (43 cases) in which both the estrogens and gonadotropins were determined, there was a decrease in the estrogen excretion and an increase in the excretion of gonadotropin in the pre-eclamptic and eclamptic groups, but the excretion of estrogen was normal and the excretion of gonadotropin increased in the hypertensive and renal disease group. Because of the extreme variability of individual values the relationship of the estrogen and gonadotropin excretions (E:G ratio) is believed to be a better index of hormone values than the twenty-four-hour excretion value for either hormone.

The values found for this group were:

1. The excretion of estrogen (Mean \pm S. E., I.U. per 24 hours) for the various groups was: normal, $38,260 \pm 5,240$; hypertensive and renal disease, $37,540 \pm 5,770$; pre-eclamptic, $17,620 \pm 3,030$; eclamptic, $11,800 \pm 3,670$.

2. The excretion of gonadotropin (Mean \pm S. E., R.U. per 24 hours) for the same groups was: normal, $12,340 \pm 2,760$; hypertensive and renal disease, $20,690 \pm 2,660$; pre-eclamptic, $24,470 \pm 3,960$; eclamptic, $76,860 \pm 31,210$.

3. The ratios of the excretion of estrogen to gonadotropin expressed as the Mean \pm S. E., for the above groups were: normal, 6.38 ± 2.13 ; hypertensive and renal disease, 2.63 ± 0.77 ; pre-eclamptic, 0.97 ± 0.23 ; eclamptic, 0.28 ± 0.08 .

Comparisons of these means by the Fisher method gave the following probabilities, P^* for significant differences between the various groups:

1. For the excretion of estrogen per twenty-four hours, these values for the different groups were: normal and pre-eclamptic, $P = < 0.01$; normal and hypertensive and renal disease, $P = > 0.9$; pre-eclamptic and hypertensive and renal disease, $P = < 0.01$.

2. For the excretion of gonadotropin per twenty-four hours in the same groups, the values were: normal and pre-eclamptic, $P = 0.03$; normal and hypertensive and renal disease, $P = 0.04$; pre-eclamptic and hypertensive and renal disease, $P = 0.43$.

3. For the estrogen:gonadotropin ratios the values were: normal and pre-eclamptic, $P = 0.01$, including the eclamptic group, $P = < 0.01$; normal and hypertensive and renal disease, $P = 0.07$; pre-eclamptic and hypertensive and renal disease, $P = 0.06$; hypertensive and renal disease and pre-eclamptic and including the eclamptic group, $P = < 0.01$.

The total group of estrogen studies (43 cases above and 14 with estrogen determinations only) gave the following values (Mean \pm S. E., I.U. per 24 hours) for the various groups: normal, $36,550 \pm 4,780$; hypertensive and renal disease, $35,580 \pm 4,490$; pre-eclamptic, $18,490 \pm 2,600$. Comparison of these means shows a significant difference between the normal and the pre-eclamptic groups ($P = < 0.01$) and the pre-eclamptic and the hypertensive and renal disease groups ($P = < 0.01$) but not between the normal and the hypertensive and renal disease groups ($P = 0.87$).

* $P = \pm 0.01$ indicates one possibility in 100 that these differences are not significant.

Methods for the quantitative assay of estrogens and gonadotropins employing dose-effect standardization curves and methods of extraction are described and discussed.

Excretion of estrogen and gonadotropin has been studied in 17 additional cases representing the following conditions: early pregnancy, hyperemesis gravidarum, abruptio placentae, hysteria with polyhydramnios and partial separation of the placenta, epilepsy, death of fetus, diabetes insipidus, diabetes mellitus, edema, achondroplastic dwarfism, and pseudomucinous cystadenoma of the ovary.

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PLASMA VITAMIN A AND CAROTENE OF THE NEWBORN INFANT*

With Consideration of Fetal-Maternal Relationships

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THE development of an accurate method suitable for clinical determinations of plasma vitamin A has opened the way for a reinvestigation of the vitamin A relationship between mother and infant. In this paper we shall present the normal vitamin A and carotene values for the cord blood of the newborn infant under normal conditions, under conditions of diminished maternal intake, and under conditions of excessive maternal intake of vitamin A. The maternal-fetal relationship of vitamin A and carotene and its bearing on the placental transmission of these substances will be considered.

Several studies reported during the past ten years have disclosed that the newborn infant differs from the adult in the amounts of vitamin A present in blood and tissues. It is well to remember that earlier workers were handicapped by intricacies and inaccuracies of a poorly understood procedure, therefore many of their detailed findings can be accepted only with reservations. As late as 1936 one of the competent investigators¹ admitted that technical difficulties were ac-

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countable for his failure to find any vitamin A in some samples of cord blood, as well as some samples of adult blood.

In 1932, Dann² studied the placental transfer of carotene and vitamin A in pregnant rats and rabbits. He observed that the vitamin A content of the fetal rat liver was small and could not be increased by giving large doses of carotene to the mother, yet large quantities of vitamin A given for a considerable length of time did increase reserve stores of the maternal and fetal livers.³ Ellison and Moore⁴ assayed the livers of newborn infants and found from 14 to 17 units of vitamin per gram of tissue, whereas the normal adult liver yielded about 220 units per gram of tissue. At about the same time Wendt¹ was analyzing blood from the umbilical cord, he was able to recover small amounts of carotene and usually very small amounts of vitamin A, but frequently he found no vitamin A. Neuweiler^{5, 6} worked concurrently but independently, and reported the presence of vitamin A in fetal organs (liver), but never did he find carotene, a fact which led him to believe the placenta impervious to the pro-vitamin. Gachtgens⁷⁻¹⁰ also regarded the placenta a partial or complete barrier, as he was able to find vitamin A in the blood of no more than 5 of 23 infants. Many of the maternal values were zero also, a type of result no longer found by improved methods of analysis. Carotene was present in all cases but the reported range of variation, as we now realize, was excessive.

The investigations of Clausen and McCoord¹¹ were important as regards carotene. They demonstrated that fetal plasma was consistently and significantly lower in carotene content than was maternal plasma. Furthermore, the plasma from the umbilical vein (containing blood flowing to the fetus) showed a greater concentration of carotene than did the plasma from the umbilical arteries (containing blood coming from the fetus). From the difference in these values the authors estimated that the fetus utilized about one milligram of carotene daily. In the same study the mean plasma vitamin A of 63 infants was found to be 12.8 "blue units" while the mean value for 32 mothers was 15.2 "blue units," a small difference. Data were not presented which correlated values for individual infants with those of their mothers, instead the authors confined their discussion to comparisons of mean values. The mean concentration of vitamin A was similar in umbilical venous blood and umbilical arterial blood, but individually some infants exhibited greater amounts of vitamin A in the arterial blood, others showed higher values in venous blood. Such individual variations, said the essayists, might be due to error of method or to transmission of vitamin A from the fetus to the placenta or vice versa.

Toverud and Ender¹² assayed the vitamin A content of livers from 47 premature infants and 50 mature infants. The average vitamin A content of livers from premature infants was greater than that of mature infants; however, the range of variation was great. When dietary history indicated maternal deficiency the vitamin A content of fetal livers was also low. When an excellent maternal dietary history was obtained, the fetal vitamin A was high. The carotene content of the fetal liver was always low.

Rehearsal of the data obtained from these several sources indicated few points of complete agreement. All agree that the infant is relatively low in vitamin A and carotene and many are of the opinion that the infant is lower than the mother. Some believe the placenta im-

pervious to carotene and others believe it impervious to vitamin A. Yet certain observers consider that carotene passes to the fetus and forms vitamin A. If a single generalization is permissible from these observations and opinions, it would be that values of vitamin A and carotene in the fetus are low compared to those of the mother, and this difference suggests some impedence in the placenta.

Procedures

Samples of blood for study were obtained at delivery in the following manner: As the infant was delivered the pulsating umbilical cord was immediately clamped and severed. Twenty-five milliliters of blood were quickly collected from the placental end of the umbilical cord. A small amount of potassium oxalate in the receptacle prevented coagulation. This specimen was a mixture of venous and arterial blood, although venous blood formed the major part of the sample, as the umbilical arteries are small and contract quickly after the cord is clamped. A 12 ml. sample of maternal blood was withdrawn from a vein immediately after the fetal sample was obtained.

Total carotene and vitamin A were determined in the plasma with the aid of the Evelyn photoelectric colorimeter according to the technic described by Kimble,¹³ which adapts to blood analysis the method of assay of the vitamin in oils published by Dann and Evelyn¹⁴ in 1938. This method for the macrocolorimeter follows the general lines suggested by May in the same year for the microcolorimeter¹⁵ and smaller amounts of plasma. Briefly, the method involves extraction of the plasma carotinoids with ethyl alcohol and petroleum ether, determination of the carotene from the amount of yellow color imparted to the ethereal extract, removal of this solvent so that the remaining material can be dissolved in chloroform, and the development of the standard Carr-Price reaction by the addition of antimony trichloride in chloroform. The reaction takes place with the tube of extract in the reading position of the colorimeter so that the light transmission at maximum density of the evanescent color can be easily and accurately determined. The results of the final reaction are corrected for the amount of color due to carotene, using the constant given by Dann and Evelyn¹⁴ for this purpose.

Recent studies in which more successfully purified preparations of carotene and vitamin A have been available for colorimetric standards indicate that some of the older constants used in calculating the results of the chemical determination of these substances will need to be changed for increased accuracy. This probability was noted in a previous publication.¹³ Thus, though the chemical procedure has become so well standardized that colorimetric readings yielded by a given vitamin-containing preparation can readily be duplicated from one laboratory to another, *interpretation* of the chemical findings in terms of units or weights of the vitamin represented still varies grossly in different hands, according to the form of calculation and expression chosen. These uncertainties involve the exact correction to be applied to the amounts of blue color formed by the carotene mixed with vitamin A in the Carr-Price reaction, and also the validity of various conversion factors that have been worked out for interchanging chemical, or "blue" units with actual weights of the vitamin, or with the biologic (International) units that were formerly the only acceptable standard of reference. Because the details of these various relation-

ships are still controversial, with most of the final answers still to be furnished, calculation formulas used in the present work have remained the same as those used earlier in the same laboratory, excepting that the vitamin A is now expressed as the more generally familiar International Units by means of conversion factors suggested for tentative use before. It is interesting that data from some other laboratories are now available for comparison. But in this connection it must be emphasized that in any work concerning vitamin A, *both* the technique of assay and the method of calculation of results must be uniform before comparisons among different sets of data can be attempted.

Accordingly, the values for vitamin A in the plasma of healthy non-pregnant women studied in this laboratory have been found to lie, for the most part, between 75 and 120 I.U. per cent. These nonpregnant controls represented essentially the same sort of population as did the mothers of the present study. The average value for 50 nonpregnant women was 96 I.U. per cent. Using the same technique and calculations, results for healthy females have averaged 95, 87, and 87 I.U. per cent in three other available reports.¹⁶⁻¹⁸

For carotene, the female controls in this laboratory varied from 95 to 350 gamma per cent (micrograms per 100 ml.) with an average level of 203 gamma per cent. Others have recorded average figures of 197¹⁶ and 227¹⁷ for their control groups of nonpregnant women.

The patients chosen for study represented a broad economic and social group. Some were indigent, some were private patients and some were of intermediate status. The patients were approximately evenly divided within the three groups. The dietary intake of vitamin A was roughly estimated by careful questioning, and it was found to be variable, but in general it followed economic and social factors. In certain instances large doses of vitamin A were administered to the pregnant women in the form of halibut liver oil.*

Results—Vitamin A

Values in the Newborn.—The plasma vitamin A values of the newborn were lower generally than those values considered normal for an adult. A series of 143 determinations were made on the plasma of normal infants delivered at term pregnancy. The lowest value recorded was 24 I.U. per 100 ml. of plasma and the highest was 79. This is in contrast to the total range of 65 to 165 I.U. per 100 ml. obtained in this laboratory for healthy nonpregnant adult women. On the basis of further evidence, values from 65 to 75 are now considered "borderline." The mean plasma vitamin A for the infants was 49 I.U. per 100 ml. with a standard deviation of 12.2 and a coefficient of variability of 25 per cent. Fig. 1 illustrates the frequency distribution of the entire series. Note that 55 of the 143 infants (39 per cent) were within the range of 40 to 50 I.U. per cent and the remainder were not distant from the mode. Seventy-five per cent (104 of the 143 infants) were within the range of 30 to 60 I.U. per cent.

Relationship of Fetus to Mother.—Evaluation of the correlation between the infants' vitamin A and mothers' vitamin A for the data as a whole indicates a simple correlation coefficient of 0.22 which might be significant for 143 observations. Further examination and subdivision of these data suggest that a spurious correlation has arisen from some extraneous reason. Hence the results probably do not represent a true

*Haliver oil furnished through courtesy of Abbott Laboratories.

correlation between the mother and infant, and this belief was substantiated by the appearance of a scattergraph (not included) which showed no gross evidence of correlation. The differences between mother and infant in magnitude and range of vitamin A values for the whole series are disclosed by the frequency distribution of Fig. 1.

Fig. 2 exhibits the individual maternal-fetal relationship of each pair arranged according to the ascending vitamin A values of the mother. The fetal values can be seen as a broad band extending across

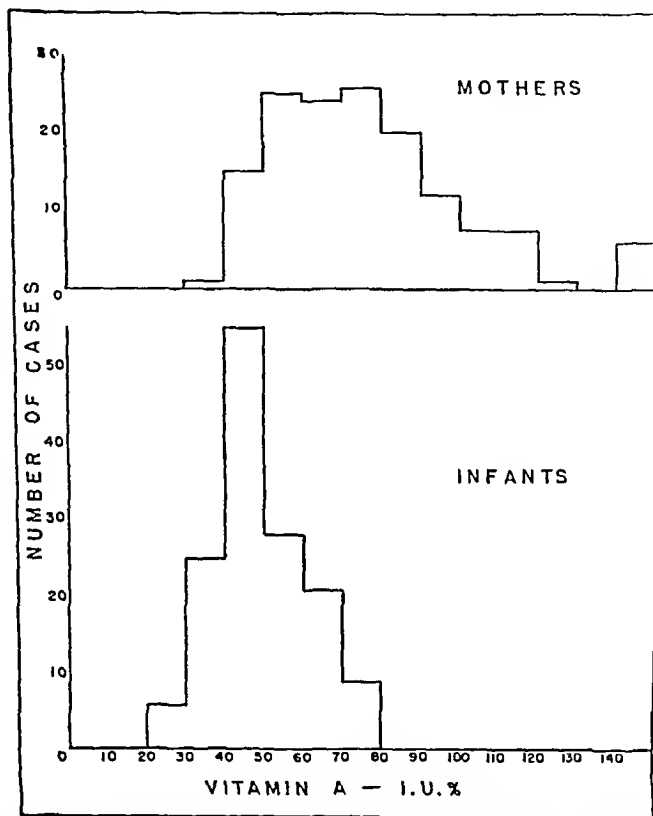


Fig. 1.—A frequency distribution graph showing the number of mothers and infants studied and the range of values of their plasma vitamin A.

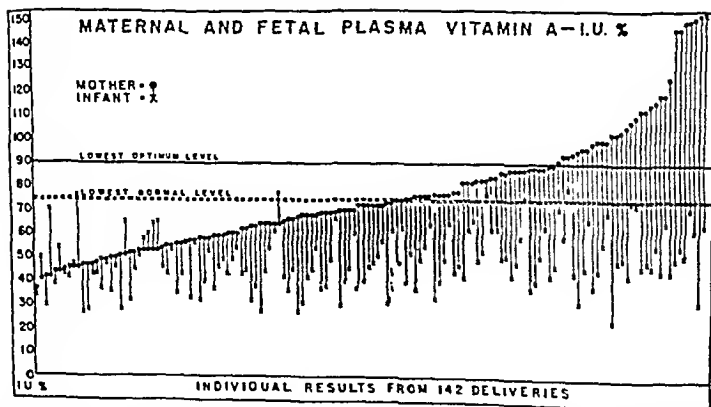


Fig. 2.—Showing the individual plasma vitamin A values for each mother and her infant. Note the presence of inverted relationships in the left half of the graph.

the entire field. Some of the highest fetal values are paired with the lowest maternal values and, conversely, some low fetal values accompany the highest maternal ones. The five highest infants had vitamin A values barely within the lower limits of what we consider a normal range for nonpregnant women; i.e., around 75 I.U. per 100 ml.

We have previously stated that under usual conditions the maternal values for vitamin A exceed those of the fetus. Further inspection of the data indicates this relationship was maintained as long as the mothers' vitamin A was normal. However, when the maternal values dropped below normal the fetal values were sometimes essentially equal to the mothers' and sometimes greater (Fig. 2). This upset we have called inversion. In the present study inversion appeared as maternal levels of vitamin A dropped below 80 I.U. per 100 ml. There were 91 mothers with vitamin A values below 80 I.U. per cent, and in 19 of these cases (21 per cent) there was inversion in the mother-infant vitamin A relationship. As the amount of maternal vitamin A decreased the frequency of inversion increased and there was "inversion" in eight cases with lowest maternal values.

When it became evident that the plasma vitamin A of the fetus remained independent of that of the mother, whether her plasma vitamin A was normal or below normal, we undertook to elevate the maternal values above normal by feeding large amounts of the vitamin during pregnancy. Moderate to large amounts of vitamin were given to nine patients for varying periods of time before parturition. Table I lists the dosages used, the duration of treatment, and the results obtained. Large doses of the vitamin elevated the maternal plasma concentration to a high level but they were without demonstrable effect on the fetus.

TABLE I.—SHOWING THE MATERNAL AND FETAL PLASMA VITAMIN A CONCENTRATION AFTER ADMINISTRATION OF MODERATE AND LARGE DOSES OF VITAMIN A

PATIENT	DAILY DOSE I.U.	DAYS OF TREATMENT	MATERNAL VITAMIN A BEFORE TREATMENT	MATERNAL VITAMIN A AT DELIVERY	FETAL VITAMIN A AT DELIVERY
MJ	20,000	98	*	76	55
BK	20,000	135	*	74	48
HJ	20,000	182	*	94	44
EF	30,000	210	*	148	52
CT	60,000	3	62	118	45
PW	60,000	12	86	113	55
MJ	60,000	32	58	149	62
DS	330,000	6	94	151	32
HS	330,000	18	72	145	55

*Comparison between values obtained early in pregnancy and values obtained at or near delivery is not permissible as will be shown in a forthcoming publication.

Miscellaneous Relationships.—Attempts were made to correlate the vitamin A of the newborn with numerous other variables apparent at birth.

A sex difference in adult plasma vitamin A has been pointed out by one of us (M. S. K.)¹³ and has been verified^{17, 18, 20} or independently noted¹⁹ by others. These investigators have found the plasma vitamin A of the adult female to be lower than that of the adult male though all do not agree on the magnitude of the difference. We were interested to determine if a sex difference in vitamin A was present at birth. Of the 142 infants examined, 67 were females with a mean

plasma vitamin A of 52 I.U. per 100 ml., 75 were males with a mean value of 47 I.U. per cent. From these averages alone one might assume that there is a reversal in infants of the sex difference found in adults. However, the difference of the means is not statistically significant. Yet the data do show that the sex difference noted in adults does not obtain in the newborn infant. An explanation in adult physiology remains to be shown.

The amount of vernix caseosa was compared with the amount of plasma vitamin A. Suitable records of 65 infants permitted classification according to the amount of vernix caseosa. The amount of vernix caseosa was not accurately measured but experience quickly enabled us to divide the infants into one of the three groups: +, scanty amounts along the folds of the skin; ++, average amounts over body surfaces; and +++, large or excessive amounts. Table II indicates the findings:

TABLE II. A COMPARISON OF THE MEAN VITAMIN A CONCENTRATION IN PLASMA OF THE FETUS AND THE AMOUNT OF VERNIX CASEOSA PRESENT AT BIRTH

NUMBER OF INFANTS IN GROUP	AMOUNT OF VERNIX CASEOSA	MEAN VITAMIN A OF GROUP I.U. %
21	+	48
16	++	48
27	+++	49
Mean for entire series		49

No correlation between vernix caseosa and amount of circulating vitamin A could be demonstrated and the average plasma vitamin A within each group was similar to the average for the series as a whole.

Five premature infants were studied. Data from so few infants are of little statistical value, yet it is interesting to note that premature infants had values for vitamin A which were below the group average and 3 of the infants were in the low range (Table III).

TABLE III. VITAMIN A, I.U. PER 100 ml. OF PLASMA IN PREMATURE INFANTS

WEIGHT IN POUNDS	GESTATIONAL AGE IN WEEKS	SEX	PLASMA VITAMIN A
2.5	26	M	37
3.0	32	F	37
3.8	34	M	34
4.0	30	M	46
4.7	30	F	47

The low vitamin A values for premature infants suggested the possibility of a relationship between maturity and vitamin A. Accurate determination of gestational age is exceedingly difficult; nevertheless, birth weight and gestational age are generally related, hence the birth weight and plasma vitamin A have been compared. A total of 147 infants were studied, including the 5 premature infants. Inspection of the data (Fig. 3) indicates some relationship between weight and vitamin A so long as the weight is below average. For example, not a single infant weighing 6½ pounds or less had a plasma vitamin A above 49 I.U. per 100 ml. The latter figure incidentally is also the mean for the entire series. The average weight of all infants was 7.5 pounds and the series was then subdivided according to weight, those above the average and those below it. Table IV summarizes the sta-

TABLE IV. STATISTICAL DATA COMPARING INFANT'S WEIGHT AND PLASMA VITAMIN A VALUES

	NUMBER OF INFANTS	MEAN VITAMIN A	MEAN WEIGHT IN POUNDS	S.D. WEIGHT	S.D. VITAMIN A	COEFFICIENT OF CORRELATION
Above 7.4 pounds	76	52	8.3	± 0.63	± 13	0.18
Below 7.4 pounds	71	45	6.4	± 0.95	± 10.5	0.28

tistical data for each weight group. Thus it would seem that low vitamin A values are related to a low birth weight, or possibly to some element associated with low birth weights.

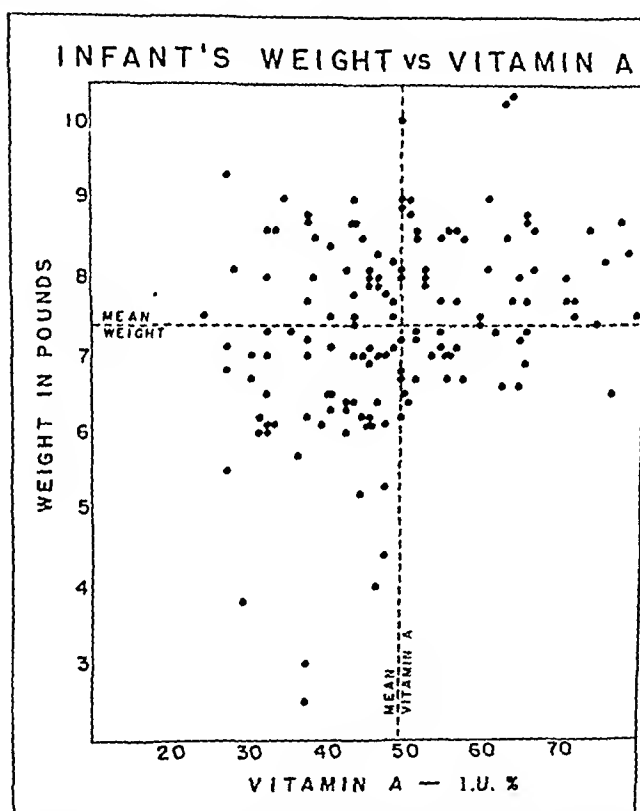


Fig. 3.—Showing the infants' weight plotted against plasma vitamin A. Note that all infants weighing less than $6\frac{1}{2}$ pounds have plasma vitamin A values in the lower range.

Plasma vitamin A determinations were made on two sets of twins. A pair of identical twins had plasma vitamin A values of 30 and 71 I.U. per cent while nonidentical twins had values of 31 and 44 I.U. per cent. Such astonishing differences were not anticipated, particularly those of the identical twins. Obviously there was not complete and free exchange of blood between the identical twins; dissection of the placental vessels revealed the presence of anastomoses between small vessels only. These wide variations noted in infants supplied from an identical source lead us to believe that some intrinsic factor of the fetus may determine the concentration of plasma vitamin A. As we shall see in a subsequent paragraph, chemical dissimilarities between twins are not limited to vitamin A.

The scope of this study does not include abnormal infants, yet the striking results from one such infant warrants mention, though no explanation is at hand. This infant was delivered at term and seemed normal. An unusually small layer of red blood cells in the centrifuged specimen of cord blood clearly indicated the presence of a severe anemia. The plasma, which was proportionately increased, had a vitamin A value of 104 I.U. per 100 ml., a value 25 per cent higher than any other in our infant records. The infant, which survived, was found to have erythroblastosis of the anemie type.

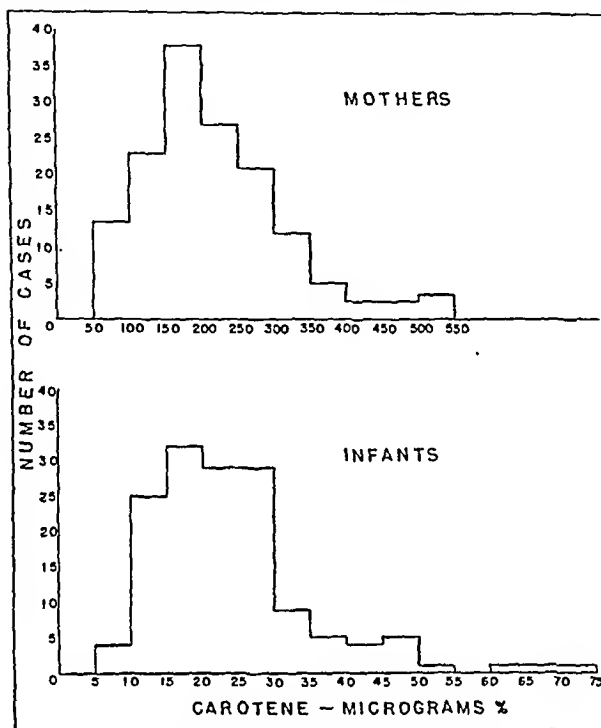


Fig. 4.—A frequency distribution graph showing the number of mothers and infants studied and the range of their plasma carotene. The scale of maternal values is ten times greater than the scale of fetal values.

Carotene

Values in Newborn Infants.—The plasma carotene of the cord blood is very low. The mean value for 149 normal infants delivered at term was 23 micrograms per 100 ml. of plasma, the lowest value recorded was 9 and the highest was 75. S.D. was 11.1 micrograms and the coefficient of variability was 48 per cent. Fig. 4 shows the frequency distribution of the entire series for the infants and their mothers. Note that the disparity in absolute levels of the two series is so great that the maternal values have been plotted on a scale ten times that for the infants. One hundred and fourteen of 149 infants (76 per cent) had carotene values between 10 and 30 micrograms per cent, which is roughly within $\pm 1 \times$ S.D. and indicates a "normal" type of distribution. Distribution in the maternal series appears "normal." The atypical high values to the right in both series represent mothers on high carotene intake.

Fig. 4 shows the frequency distribution of maternal and fetal values. For reasons mentioned in the preceding paragraph, the fetal values are

on a scale of one-tenth the maternal values in order to get a comparable plot. The shape of the curve of maternal values appears to be more "normal" than the curve of fetal values, but this could be explained by the difference in scale. Inherent error of our method for the determination of carotene is on the order of ± 2 micrograms per 100 ml. Such a small error would not change the distribution of maternal values significantly, but it might well change the distribution of fetal values where the difference between groups is only 5 micrograms.

Miscellaneous Relationships.—The fetal carotene values and the fetal-maternal relationships did not deviate significantly under conditions of prematurity or multiple pregnancy.

Relation of Vitamin A and Carotene.—Carotene is the precursor of vitamin A and can be converted into vitamin A by the human body. The relationships between these two substances in the adult are complex and no correlation between the two can be demonstrated in human plasma.¹³ In case the situation might be simpler in the infant, an effort was made to determine any relationship which might exist between carotene and vitamin A in the fetal plasma and this comparison was possible in a series of 133 cases. Correlation was lacking, as was the case with adults. This is demonstrated in Fig. 6. For example, it is possible to find low plasma vitamin A associated with either high or low plasma carotene, and conversely, a high plasma vitamin A might be combined with either high or low plasma carotene.

Discussion

Vitamin A.—The data from this study indicate that the normal infant is born with an exiguous supply of blood vitamin A, exiguous in the sense that a normal infant at birth has less vitamin A circulating in the blood than does its normal mother. This relationship extends to the tissues as well, for the fetal liver contains less vitamin A than the maternal liver.⁴ Nevertheless, these low concentrations of vitamin A do not necessarily signify deficiency; rather they will need to be considered as the physiologic condition of the newborn infant.

The mode of the present series was from 40 to 50 I.U. per 100 ml. and included approximately 40 per cent of all infants, while a range of 30 to 70 I.U. per cent included approximately 90 per cent of all infants. For purposes of comparison the range of normal adult female values, as we have said, lies between 75 and 120 I.U. per cent. So long as the mother remains within this range her fetus may be expected to have values approximately one-half as high.

Relationship of Fetus to Mother.—In spite of the very low fetal plasma carotene it has a demonstrable direct relation to maternal carotene. Fig. 5 shows the fetal values plotted against the corresponding maternal values. Correlation is obvious by inspection alone. The multiple correlation coefficient of the entire series was 0.71, which appears to be highly significant. By statistical criteria, a somewhat curvilinear regression was found to describe the series slightly better than a straight line, and the following formula was derived: $IC = 4.06 + 0.0636 MC + 0.0001 MC^2$. When the values for maternal carotene, MC, are known, corresponding values for the infant, IC, can be estimated by the above formula. As a convenient rule of thumb the

fetal value may be estimated as one-tenth the maternal value, if the latter is within the middle range (Fig. 5). If maternal values fall in the low range the fetus has approximately one-eighth as much carotene and when maternal values are high the fetus has about one-twelfth as much carotene.

There was no correlation between the values of maternal and fetal plasma vitamin A. This lack of correlation suggests that the amount

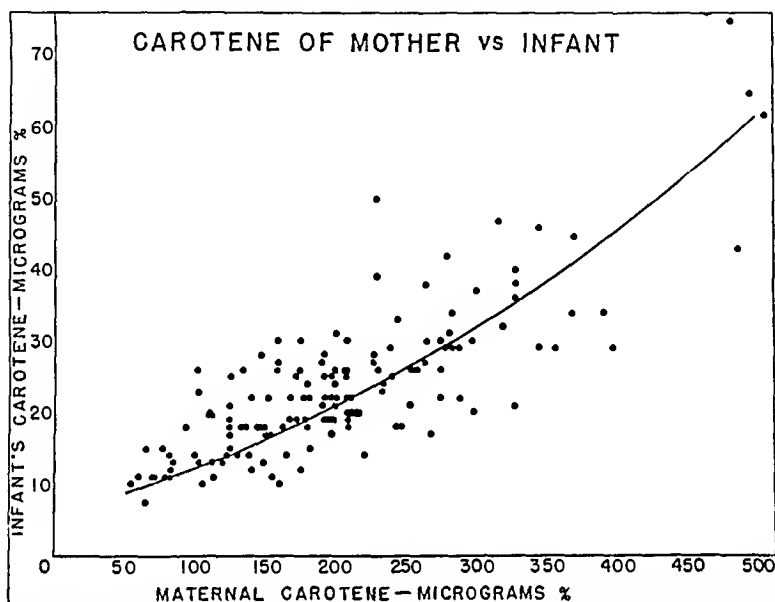


Fig. 5.—Scattergraph showing plasma carotene values of fetus plotted against the similar values for the mother. The line expresses the equation listed in the text.

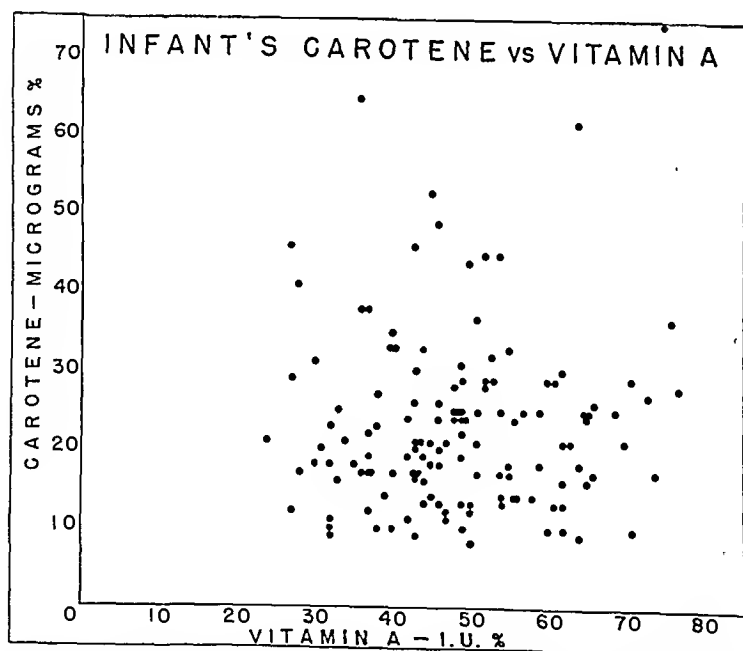


Fig. 6.—Showing infants' carotene values vs. plasma vitamin A values. There is no evidence of correlation.

of vitamin A in the fetal circulation is independent of the amount in the maternal circulation. The independence of the fetus in this respect was demonstrated in several ways:

First, there was inversion of the usual maternal-fetal relationship. Obviously inversion cannot occur until the maternal range of values has dropped below the level of highest fetal values. Inversion was limited to the range of subnormal maternal values and was manifested by the appearance of fetal values which sometimes equalled or exceeded those of the mother. It is probably fortuitous that inversion in the maternal-fetal relationship and subnormal adult values appeared simultaneously at maternal levels below 75 to 80 I.U. per cent. The frequency of inversion increased as maternal values decreased, a conclusion well illustrated by our data from the ten women with lowest values; eight of these women had inverted values. What the status of the maternal-fetal relationship would be under conditions of extreme maternal deficiency is a matter for interesting speculation. If the maternal level of vitamin A dropped below 24 I.U. per 100 ml., the lowest fetal value recorded by us, would all fetal values be higher? Speculation aside, our data demonstrated that the plasma vitamin A values of the infant are independent of the maternal values when the latter are in the range of deficiency.

The fetal values are equally independent of those of the mother under conditions of excessive vitamin A intake. Both moderate and large doses of vitamin A elevated the maternal blood plasma vitamin A to high levels, yet the fetal plasma vitamin A was not influenced.

Additional evidence of fetal independence was disclosed by the study of twin pregnancies, where wide variations were unexpected and unexplained. Boyd,²¹ however, has noted similar wide variations in blood lipids of twins and we have also noted such variations in carotene and vitamin C. We are left with the unsatisfactory answer that such variations are inherent to the fetus as twin infants certainly have an identical maternal source of supply and the same placental barrier. These variations are probably associated with the distribution and utilization of supplies offered, and attention is called to the marked variation in weights of identical twins as another example of such a condition.

We therefore conclude that the fetus and mother are never in equilibrium as regards plasma vitamin A, excepting by chance. Furthermore, our evidence suggests that there may be little or no transmission of vitamin A through the placenta in either direction. If there is placental transmission it is not related to the amounts of vitamin A circulating in the maternal blood, but must be determined or limited by some intrinsic fetal factors.

The weight of the newborn infant is one factor associated with the plasma vitamin A of the cord blood; weight is also associated with deposition of fats which takes place late in gestation.²² Our data

indicated a significant relationship between weight and vitamin A in infants below normal weight. Is it possible that this relationship may be associated with metabolism of fats? Boyd²¹ has studied the placental transmission of three general groups of fats: (1) the phospholipids, which apparently pass the placental barrier with ease and are utilized by the infant in rather large amounts; (2) the cholesterol, which are present in smaller amounts and are apparently not so readily transmitted or utilized; and (3) the neutral fats, which sometimes pass the placental barrier, but may be synthesized by the fetus. Laseh²³ reported that vitamin A was associated with cholesterol and neutral fat, and recent investigators including Josephs²⁴ are of the opinion that both vitamin A and carotene, being fat soluble, are closely concerned with lipid chemistry. The type and amount of lipid with which vitamin A is associated and the ease or difficulty with which this combination of lipid and vitamin pass the placental barrier may be a determining factor in the fetal concentration of vitamin A. Further investigations along these lines are clearly indicated.

Straumfjord²⁵ suggested that the formation of vernix caseosa might be a manifestation of vitamin A deficiency. By prolonged administration of large doses of the vitamin to the mother he was able to reduce the frequent appearance of vernix caseosa in newborn infants. No blood determinations of vitamin A were made. In our series, which included blood determinations, we were unable to obtain any evidence of correlation between the plasma vitamin A of the fetus or its mother and the amount of vernix caseosa, even when the maternal values suggested moderate deficiencies.

No interpretation is offered for the fact that one infant with erythroblastosis and congenital anemia had by far the highest vitamin A value recorded for fetal plasma in our study.

Carotene.—The carotene concentrations in blood of the newborn infant are very low and are always much less than those of the mother. Yet in spite of this disparity, there is a definite relationship between the fetal and maternal values throughout the entire range of values. Fetal plasma concentrations were approximately one-tenth as high as maternal concentrations when the latter were average, one-eighth when the mothers' were low, and one-twelfth when the mothers' were high. This intimate relationship suggests a small but regular transfer of carotene from the mother to the fetus, and is in distinct contrast to independence of the mother and fetus as regards plasma vitamin A. We have no evidence to explain the physiologic differences of transmission of these two substances through the placenta, but we believe that differences in lipid solubility may be one of the important factors.

If the fetus does not receive vitamin A from the mother, there is but one other logical source: synthesis from carotene. The small but regular transfer of carotene from mother to fetus suggests this possibility. Yet the relationship can be traced no further as there is no

apparent correlation between the levels of carotene, either fetal or maternal, and fetal plasma vitamin A. This failure to show correlation does not necessarily invalidate the above suggestion for we know that the normal adult synthesizes vitamin A from carotene and still there is no demonstrable correlation between plasma carotene and plasma vitamin A.¹³

Two aspects of this research concerning vitamin A are significant clinically: one is the apparent independence of the fetus as regards plasma concentrations of the vitamin; the other is the comparatively small amounts of vitamin A found in the plasma of the newborn infant.

It has long been said that the fetus lives as a parasite upon its mother and adequate fetal nutrition is usually maintained in the presence of maternal starvation. Our data suggest a similar relationship for vitamin A because the fetus maintained values for the vitamin within a moderate range regardless of mild or moderate maternal deficiencies. In such degrees of deficiency we need not concern ourselves with the state of the fetus for as far as the *fetus* is concerned there would seem to be no advantage in giving the mother excessive amounts of vitamin A, for we were unable to elevate the fetal plasma vitamin A under such conditions.

The same statement does not obtain for carotene. Maternal carotene deficiencies are reflected by the fetus as are maternal carotene excesses, although concentrations in the fetal blood are always much less than those of the mother. Although our knowledge of carotene metabolism is incomplete we can say that the fetus is dependent on the mother for an adequate amount of carotene which can be supplied by a diet adequate in yellow and green leafy vegetables.

The infant is born with a small complement of vitamin A and should be assured of an adequate intake during early prenatal life. This is particularly true of infants of subnormal weight. Under ordinary conditions the only source of vitamin A during the first few weeks of life is human or cow's milk. Human colostrum and early breast milk contain adequate amounts of vitamin A and constitute the ideal source of supply. Cow's milk, which contains smaller amounts of vitamin A, is often used as a substitute for the human product. Such substitution is undesirable during the first two weeks of life but if it is absolutely necessary the addition of vitamin A to the cow's milk is clearly indicated.

Summary and Conclusions

1. The values obtained by a reliable method of chemical analysis for plasma vitamin A of normal newborn infants were approximately one-half as high as normal adult values.

2. Plasma vitamin A of the newborn infant was independent of maternal plasma vitamin A regardless of the mother's intake of this vitamin. Low maternal values were not reflected by the fetus, and in many such instances the fetal values were similar or higher. Adminis-

tration of excessive amounts of vitamin A to the mother elevated the maternal blood values but was without effect on the fetal blood values.

3. Plasma vitamin A of infants below average weight was usually low, while that of infants above average weight varied within the normal range for infants.

4. Plasma carotene from the umbilical cord of newborn infants was approximately one-tenth as high as maternal plasma carotene when the latter were average, one-eighth when the maternal values were low, and one-twelfth when they were high.

5. Fetal plasma carotene varies regularly with maternal plasma carotene and can be estimated with considerable accuracy by a mathematical equation showing a curvilinear relation.

6. There was no correlation between fetal plasma carotene and vitamin A, yet this does not necessarily exclude carotene as a precursor of fetal vitamin A.

7. Vitamin A, in contrast to carotene, either is not transmitted or is poorly transmitted from the mother to the fetus. In this respect it resembles certain lipids, and vitamin A transmission through the placenta may be related to or limited by lipid metabolism at the placental barrier.

8. The newborn infant should be assured of an adequate supply of vitamin A during early life. Human colostrum and early breast milk are the ideal source of supply, but if cow's milk is substituted there is need for additional vitamin A.

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THE ACTION OF SYNTROPAN ON THE UTERUS*

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IT HAS been reported that syntropan (the phosphate of the dl-tropic acid ester of 3-diethylamino-2, 2-dimethyl-1-propanol) hastens the first stage of labor in the human being.¹⁻⁶ This drug is claimed to effect an increase in the rate of dilatation of the cervix and it is implied that the principal mechanism is one of accelerated cervical relaxation.

Studies of the action of syntropan on experimental animals have revealed that this drug causes contraction of the intact uteri of non-pregnant and pregnant rabbits.⁷ It has also been shown that syntropan causes contraction of uterine strips from nonpregnant rabbits; non-pregnant guinea pigs; nonpregnant cats (pregnant cat uteri were relaxed by syntropan); and nonpregnant human beings.^{7, 8, 9}

The purpose of the present investigation was (1) to confirm and extend certain of the existing information on the action of syntropan on the excised uterine strip; (2) to study the action of syntropan on the intact animal uterus; and (3) to obtain information on the action of syntropan on the intact, unanesthetized, pregnant animal prior to spontaneous delivery.

Method

The action of syntropan** on the uterine strip has been studied in nonpregnant, pregnant, and post-partum rats; nonpregnant, pregnant, post-partum, and progesterone treated nonpregnant guinea pigs; and pregnant human beings. The progesterone treated strips were obtained from non-pregnant guinea pigs which were injected subcutaneously with 5.0 mg. of progesterone in oil† daily for five days. These uteri were studied on the eighth day, and at this time showed marked endometrial growth. The human uterine strips were obtained at the time of elective cesarean section in patients who were not in labor.‡

Strips of the various uteri were suspended in a small bath (7.5 c.c.) containing a modified Sollmann-Rademaekers solution (NaCl 9.0 Gm./L.; CaCl₂ 0.12 Gm./L.; KCl 0.423 Gm./L.; NaHCO₃ 0.32 Gm./L.; and dextrose 0.5 Gm./L.). The bath was maintained at 38° C., and the solution was constantly aerated.

The syntropan was made up to 1 per cent strength in portions of the above solution, and was kept at the same temperature as the bath.

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†Furnished to us by Roche-Organon, Inc., through the courtesy of Mr. E. W. Marti and Mr. W. P. Freeman.

‡Furnished to us through the courtesy of Dr. B. Mortimer.

In most instances enough of this 1 per cent syntropan was added to the bath to make the final concentration 1:3,000.

Studies have been carried out on the change of pH of the bath as produced by syntropan. A glass electrode pH meter was employed. In the control procedure, in which the pH was altered by the same amount as by syntropan, dilute hydrochloric acid was employed.

Studies of the action of syntropan on intact post-partum uteri have been performed on immediately post-partum (within 48 hours) guinea pigs and dogs. Sodium pentobarbital anesthesia was employed, and the activity of the uteri was recorded by means of balloon water manometer systems.

In the guinea pigs the balloon was introduced into the uterus by way of the vagina. In the dogs the abdomen was opened and one balloon was introduced into the body of the uterus by way of a small incision in the wall of the uterus, and another balloon was placed in the cervix. This latter balloon was of a cylindrical type with rigid metal ends so arranged that only a circular type of movement was recorded.

Injections of syntropan (2 to 20 mg./kg.) were made intravenously; via the jugular vein in the guinea pig, and via the femoral vein in the dog.

Studies of the action of syntropan on pregnant unanesthetized animals were performed on guinea pigs and rats. Dated pregnancies were obtained by the following techniques. It is well known that the rat and the guinea pig exhibit a more or less uniform estrus cycle. The period of estrus in the guinea pig is grossly characterized by solution of a membrane which at all other times seals the vagina. Therefore, dated pregnancies were obtained in guinea pigs by the simple procedure of placing males with females for only one of these periods when the vagina was open. In our colony of guinea pigs the duration of vaginal canalization was approximately three days. Therefore, if it is assumed that fertilization occurred on the middle day of vaginal opening, then the recorded duration of gestation can be in error by only plus or minus half of the period of vaginal opening in any given animal.

In the rat the technique of obtaining dated pregnancies was one of repeated breeding of the colony at two-day intervals. Feti are readily palpable on the fourteenth but not on the twelfth day of gestation. Therefore, it is felt that by this technique the duration of gestation can be determined with an accuracy of one day.

Normal gestation periods were determined in a series of rats and guinea pigs, and using these average values for reference standards treatment was carried out in other series of animals at uniform intervals prior to spontaneous delivery. In general, treatment was begun in the guinea pigs six days, and in the rats four days before the calculated delivery date.

In the guinea pig it is known that there is a marked separation of the symphysis pubis which occurs from one to several days prior to spontaneous delivery.^{10, 11} As an additional check, careful palpation of the treated animals in the present study revealed that no such separation had occurred at the time of treatment.

Treatment of the guinea pigs consisted of the intraperitoneal injection of 1 c.c. of a 1 per cent syntropan solution every half-hour for a series of ten injections, or a total dose of 100 mg. In a second series of animals comparable subcutaneous injections of syntropan were per-

formed. In a control series of animals 0.9 per cent sodium chloride rather than syntropan was injected intraperitoneally. Treatment of the rats consisted of a series of eight half-hourly intraperitoneal injections of 1 c.c. of 1 per cent syntropan solution.

All injected animals were observed for a period of 24 hours from the beginning of the injections and deliveries were recorded as those which occurred within the 4.5-hour treatment period and those which occurred during the subsequent 19.5 hours. Any deliveries which occurred more than 24 hours from the time of injection were disregarded because of the encroachment in time upon the range of observed spontaneous deliveries in the control series of animals. However, in the control series no animals had spontaneously delivered by this time.

Results

Studies of the In Vitro Action of Syntropan.—Syntropan in a concentration of 1:3,000 produced a variable response of the uterine strips. In each instance either contraction or relaxation of the strip in response to this drug was observed, but the direction of the response was constant for any given strip.

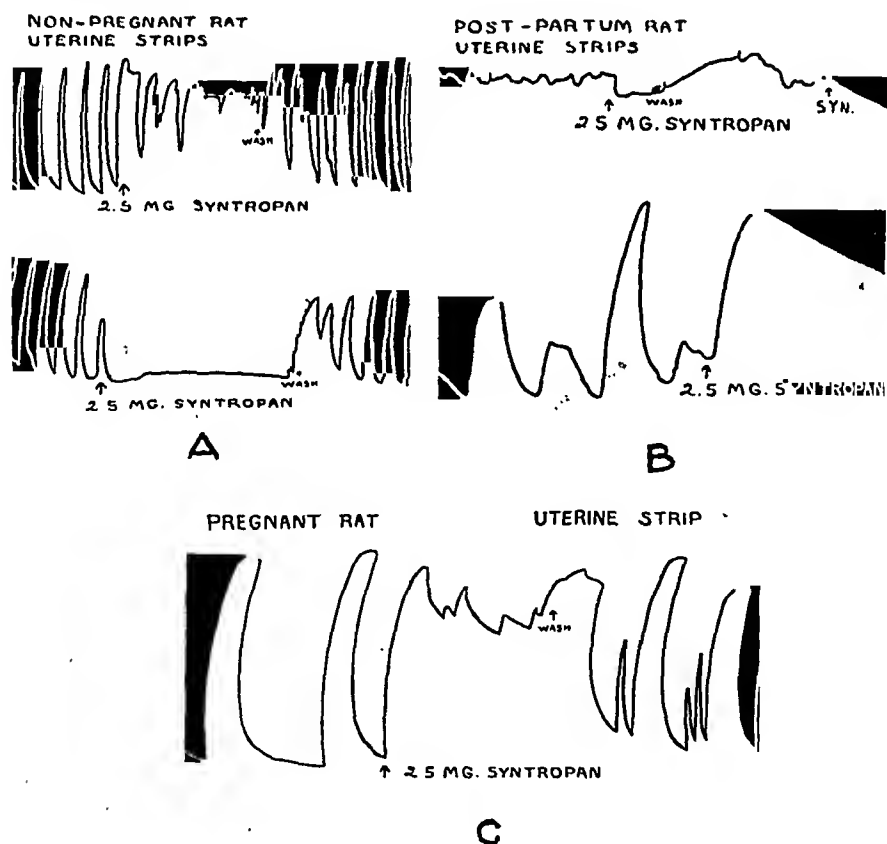


Fig. 1.

Relaxation in the present studies implies either an elimination of spontaneous contraction with a progressive loss of tone, or in certain instances, simply a cessation of spontaneous activity. In all cases spontaneous activity returned when the syntropan was washed from

the bath. Contraction implies either a single prolonged contraction with tone remaining above the basal level or an increase in frequency of contraction with an elevation of tone.

Rats.—It can be seen (Table I) that in a series of uterine strips from 9 nonpregnant rats, 4 were relaxed and 5 were contracted by syntropan (Fig. 1-A). Uterine strips from 10 pregnant rats were all contracted by syntropan (Fig. 1-C). In a series of 6 uterine strips from post-partum rats (1 to 1.5 days), 3 were relaxed and 3 were contracted by syntropan (Fig. 1-B).

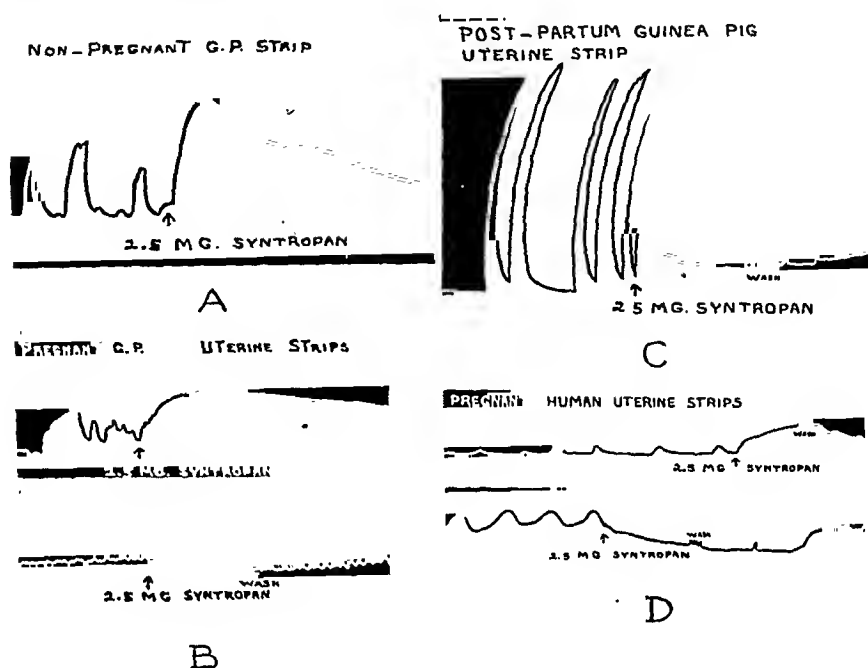


Fig. 2.

TABLE I. ACTION OF SYNTROPAN ON EXCISED UTERINE STRIPS

TYPE OF ANIMAL	TYPE OF UTERUS	NO. OF ANIMALS	RESPONSE	
			RELAXATION	CONTRACTION
Rat	Nonpregnant	9	4	5
	Pregnant	10	0	10
	Post-Partum	6	3	3
Guinea pig	Nonpregnant	10	0	10
	Pregnant	10	3	7
	Post-Partum	11	9	2
	Progesterone Treated Nonpregnant	7	0	7
Human	Pregnant	9	4	5

Guinea Pigs.—In the guinea pig (Table I) a series of uterine strips from 10 nonpregnant animals were all contracted by syntropan (Fig. 2-A). In a series of uterine strips from 10 pregnant animals, 3 were relaxed and 7 were contracted by syntropan (Fig. 2-B). In a series of uterine strips from 11 post-partum guinea pigs, 9 were relaxed (Fig. 2-C) and 2 were contracted by syntropan.

An attempt was made in a series of seven nonpregnant guinea pigs to determine whether the response of the isolated uterus to syntropan could be altered by the administration of progesterone. However, even

delivery was $66.1 \pm 3.42^*$ days from the assumed day of fertilization. None of these animals delivered before the sixty-second day. In a similar series of normal rats the average delivery date was 22.0 ± 0.7 days from the assumed day of fertilization.

It can be seen (Table II) that in a series of seventeen guinea pigs injected intraperitoneally with saline 59.6 ± 3.0 days after the assumed day of fertilization, no animals delivered within the 4.5-hour treatment period. However, eleven or 64.7 per cent of these animals delivered within the next 19.5-hour period. In a comparable series of thirty-three guinea pigs injected intraperitoneally with a total of 100 mg. of syntropan 58.4 ± 2.15 days after the assumed day of fertilization, sixteen or 48.5 per cent delivered within the 4.5-hour treatment period. Seven animals or 21.2 per cent delivered during the ensuing 19.5 hours, making a total of 69.7 per cent delivering within the 24-hour period.

TABLE II. ACTION OF SYNTROPAN ON THE PREGNANT ANIMAL

TYPE OF ANIMAL	SERIES	NO. OF ANIMALS	AVG. DURATION OF GESTATION AT TIME OF TREATMENT (DAYS)	ROUTE OF INJECTION	ANIMALS DELIVERING					
					WITHIN 4.5 HOURS		WITHIN NEXT 19.5 HOURS		TOTAL	
					NO.	%	NO.	%	NO.	%
Guinea pig	Untreated controls	18	60.0*	--	0	0	0	0	0	0
	Saline controls	17	59.6 ± 3.0	Intraperitoneal	0	0	11	64.7	11	64.7
	Syntropan	33	58.4 ± 2.15	Intraperitoneal	16	48.5	7	21.2	23	69.7
	Syntropan	12	59.8 ± 2.28	Subcutaneous	1	8.3	2	16.7	3	25.0
Rat	Untreated controls	20	18.0†	--	0	0	0	0	0	0
	Syntropan	12	18.0 ± 0.84	Intraperitoneal	0	0	2	16.7	2	16.7

*Avg. Gestation Period = 66.1 ± 3.42 days.

†Avg. Gestation Period = 22.0 ± 0.7 days.

In a series of twelve guinea pigs injected subcutaneously with a total of 100 mg. of syntropan 59.8 ± 2.28 days after the assumed day of fertilization, 1 animal delivered during the ensuing 19.5 hours, making a total of 25 per cent delivering during the 24-hour period following the beginning of injection.

In a series of twelve pregnant rats which were injected intraperitoneally with a total of 80 mg. of syntropan (Table II), no animals delivered within the treatment period. However, two animals, or 16.7 per cent, delivered within the following 19.5 hours.

Discussion

The present findings are in agreement with those of others who claim that syntropan causes contraction of the nonpregnant guinea pig uterus in vitro.^{8, 9} Contraction in response to syntropan was also uniformly obtained with pregnant rat uterine strips. However, the possibility that this drug could cause either contraction or relaxation

*The standard deviation of the distribution was calculated by the formula:

$$\sigma = \sqrt{\frac{\sum X^2 - Mx^2}{N}}$$

of the other types of uterine strips tested has not heretofore been mentioned. The mechanism by which a drug can produce opposite phenomena in one and the same type of uterine strip is not at the present time explainable, but a similar situation is known to exist in the case of the action of epinephrine on the uterine strip.¹²

The suggestion has been made that syntropan produces a response of the isolated muscle because it lowers the pH of the bath.⁹ The present observations indicate that syntropan is capable of lowering the pH of the bath at the time that the characteristic response of the muscle occurs. However, while an equal lowering of the pH by the addition of a small amount of acid is associated with a slight change in the activity of the muscle, it by no means produces the characteristic muscular response of the drug.

Whatever the final interpretation may be, the evidence indicates that syntropan has an action on the isolated uterine strip. Such evidence would suggest that syntropan may produce its effect in the animal by direct muscular action rather than by blocking a cholinergic mechanism.

It is known that experimental alteration of the hormone level of certain animals will change the response of the uterine strip to certain drugs acting on the uterus.^{13, 14} However, the present inability to alter the response of the nonpregnant guinea pig uterus to syntropan by pretreatment of the animal with progesterone is in agreement with similar observations on the rabbit.⁷

The implication found in the clinical literature that syntropan hastens cervical dilatation by relaxing the cervix does not receive support from the present observation that this drug does not relax the cervix of the post-partum dog. While there is no reason to assume that the two situations are in any way comparable, there is also no reason to assume that an increased rate of cervical dilatation can be accomplished only by a specific relaxation of the cervix. In all probability cervical dilatation is a physiologic adjustment to the presenting part and is accomplished by effective contractions of the body of the uterus. Therefore, it would appear that hastening of cervical dilatation might best be accomplished by a drug which increased the effectiveness of the contractions of the body of the uterus.

The present observations that a small per cent of guinea pigs delivered offspring following the subcutaneous injection of syntropan, coupled with the fact that a substantial number of animals delivered during a series of intraperitoneal injections of this drug, might seem to indicate that this drug is capable of inducing labor before normal term in these animals. However, the finding that a similar substantial number of animals delivered following the intraperitoneal injection of saline, but after a longer time interval, would seem to indicate that syntropan acts to speed materially the nonspecific induction of labor produced by repeated intraperitoneal injection of the guinea pig.

Summary and Conclusions

1. Uterine strips respond to the administration of a 1:3,000 dilution of syntropan. Contraction in response to syntropan occurs in non-pregnant guinea pig and pregnant rat uterine strips. Either contraction or relaxation in response to syntropan occurs in nonpregnant and post-partum rat; pregnant and post-partum guinea pig; and pregnant human uterine strips. Such evidence would suggest a direct muscular action of this drug in the animal.

2. The slight alteration of the pH of the muscle bath produced by the addition of syntropan is not responsible for the characteristic action of this drug on the uterine strip.

3. Progesterone treatment of the nonpregnant guinea pig does not alter the response of a strip of its uterus to syntropan.

4. The intravenous injection of syntropan causes a temporary increase in the contractions of intact post-partum guinea pig and dog uteri. The cervix of the post-partum dog uterus is not relaxed by syntropan.

5. Syntropan in suitable concentrations significantly accelerates the nonspecific induction of labor produced by repeated intraperitoneal injection of the pregnant guinea pig. However, a similar phenomenon does not occur to any significant degree in the pregnant rat.

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A TWENTY-SIX-DAY HUMAN EMBRYO*

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IN RECENT years there has been a reawakening of interest in the early stages of human embryology. While we were formerly dependent for our knowledge on the accidental discovery of a small number of human specimens, few of which were perfect, and many of which were incomplete or defective, recent well-planned search has resulted in the description of a relatively large series of fertilized ova, the youngest of which is beginning the process of nidation. Renewed interest in this important subject can be attributed largely to the efforts of Roek and Hertig¹ in cooperation with the Department of Embryology of the Carnegie Institution of Washington.² These workers have discovered and described twelve early human ova varying in age from 7½ to 16 days, and moreover in each instance, have supplied the data dealing with the clinical background relating to each specimen. This study has cast important light on the time of ovulation and fertilization and has demonstrated that, occasionally, visible uterine bleeding of variable quantity and duration may accompany the process of nidation.

The specimen which is to be presented is quite elderly in comparison to those of Roek and Hertig. Nevertheless it is of interest because it has been pronounced perfect and because it casts some light on the causation of uterine bleeding occurring in the early months of pregnancies which otherwise pursue a normal course.

Before presenting this specimen a few words should be said as to the manner in which it was obtained.

Mrs. M. C., 37 years old, para vii, gravida viii, was admitted as an emergency case to the obstetric service of Bellevue Hospital on Jan. 7, 1941, in the eighth month of pregnancy, complaining of headache and loss of vision. On examination she showed marked generalized edema, a blood pressure of 235/130, and a hemorrhagic retinitis. Her urine boiled solid with albumin. After a short period of observation, labor was induced by rupture of the membranes through a partially dilated, soft, thin cervix, and by the administration of pituitrin. After a short labor, she was delivered of a normal 5½ pound premature infant which survived. Following delivery, gradual improvement took place in the mother, the retinitis clearing up, but a moderate degree of hypertension and albuminuria persisting up to the time of discharge.

*Presented at a meeting of the New York Obstetrical Society, March 9, 1943.

Post-partum sterilization was considered but the idea was abandoned because of the somewhat precarious condition of the patient. Because she had five living children and had shown evidence of toxemia in some of her other pregnancies, she was given contraceptive advice, strongly warned against the danger of any further pregnancies, and was requested to report to the hospital at once if ever she suspected herself to be pregnant.

Recalling the latter advice, she returned to the hospital on Sept. 23, 1942, stating that her last menses had occurred on August 18, and that she believed herself to be pregnant. Although she appeared older than her stated age, her general physical examination was negative except for a few findings. Her blood pressure, which had been found to be 210/130 before admission, dropped to 140/100 after twenty-four hours' rest in bed. On bimanual examination the uterus felt soft and a little enlarged. The urine showed a trace of albumin. After discussing the situation with the patient, she agreed to the removal of her uterus as the most certain method of terminating the present pregnancy and preventing a recurrence of this situation. Accordingly on Sept. 25, 1942, thirty-eight days after the last menses, a high supravaginal hysterectomy was performed, leaving a small part of the lower corpus so that menstruation would continue. Her postoperative course was uneventful and she was discharged on October 8, 1942.



Fig. 1.—Nidation site ($\times 2$). The smooth mound, under which lies the ovum, measured 2 cm. in diameter. The surrounding decidua vera shows an uneven surface marked by furrows and crypts. The point at which it joins the decidua capsularis is marked by a sulcus which almost surrounds the nidation site. Note areas of discoloration in decidua capsularis. Regular network of lines on decidua capsularis is due to gauze being laid over fresh specimen during process of fixation.

The specimen was examined immediately on removal and consisted of the upper $\frac{3}{4}$ of the uterine corpus. It appeared slightly bluish in color, a little enlarged and softened in consistency. The uterus was opened by the method advised by Hertig in order to avoid injury to the contained ovum, an incision being made through the depth of the myometrium along the left border of the organ to the left cornua and across the fundus to the right cornua. The incision was completed by dividing the decidua with a pair of fine scissors. The uterus was then laid open much as one would open a book. The myometrium appeared to be slightly increased in thickness and the cavity was lined with a

pale mucous membrane 8 to 9 mm. in thickness, the surface of which was made irregular by low polypoid projections separated by crevices and furrows. The ovum was easily detected on the middle of the posterior wall to the left of the midline. Here was noted a low mound about 2 cm. in diameter projecting slightly above the surrounding decidua. The central portion of this structure showed a smooth, semi-translucent surface and was bluish in color. The borders were indistinct, merging gradually with the surrounding decidua vera, the beginning of which was marked by a crevice which seemed to encircle the nidation site. The specimen was placed immediately in Bouen's solution and allowed to fix for twenty-four hours. At the end of this time, a square block was excised from the uterine wall including the nidation site and the surrounding decidua vera (Fig. 1). The outer layers of the myometrium were cut away and the specimen was allowed to fix for twenty-four hours more. It was then placed in 80 per cent alcohol and sent to the Department of Embryology of the Carnegie Institution of Washington. Through the kindness of George W. Corner, this specimen was placed in the hands of Chester Henser for detailed study. The following is based on his report.



Fig. 2.—A portion of the amnion has been removed disclosing the embryo which measured 5.3 mm. in length. The large round structure adjacent to the amnion is the yolk sac. ($\times 8$.)

The ovum, submerged in 80 per cent alcohol, was dissected under the binocular microscope. At various steps during the progress of the work, stereophotographs were taken in order to preserve an adequate record of the relationships. A small piece of the decidua capsularis with the underlying chorionic wall was first excised in order to determine the position of the embryo. The extra-embryonic space within the chorionic plate was found to be filled with rather dense coagulum. Some of this material was carefully removed, bringing into view the yolk sac. The embryo, enclosed in the slightly expanded amnion, was next found attached to the usual site; that is, to the deep part of the inner aspect of the chorionic plate. Due to precipitation

of the proteins on the external surface of the amnion, the body of the embryo could be seen only faintly. It seemed best, therefore, to dissect off enough of the amnion to expose the body stalk (Fig. 2). The latter structure was then cut across close to the chorionic wall and the embryo and yolk sac were removed. The embryo appeared entirely normal and symmetrical. It was strikingly similar to a monkey embryo of $26\frac{3}{4}$ days' fertilization age and measured 5.3 mm. in its maximum length. The arm buds were definite and the leg buds were just appearing (Fig. 3). The embryo was embedded by the double colloidin-paraffin method and has been sectioned at 6 microns by the water-on-the-knife procedure. These sections are at present being studied.

The empty chorionic sac with its surrounding decidua was returned to the pathologic laboratory at Bellevue Hospital where additional sections were prepared in order to study the relationship of the chorion to the decidua. The details of these sections are best shown by Figs. 4 to 9.

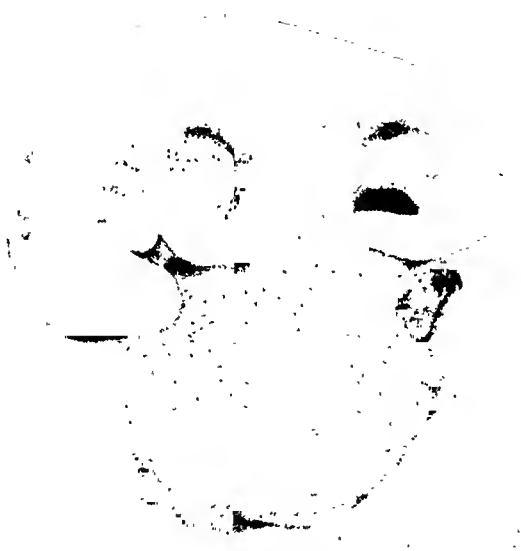


Fig. 3.—Embryo and yolk sac, lateral aspect. Note beginning limb buds. ($\times 12$.)

Discussion

Two points may be raised in the discussion of this specimen. The first has to do with the duration of the pregnancy. Dr. Heuser was able to state by comparison with a monkey embryo that the age was about $26\frac{1}{2}$ days. Granted that this deduction was correct, the day of fertilization must have been August 31, the twelfth day after the beginning of the last menses. This date would coincide with the beginning of the portion of the menstrual cycle during which ovulation is believed to occur most commonly and when fertilization of the ovum is therefore most possible. His estimation of the age by comparison and the possible age as calculated from the menstrual history, therefore, are closely similar.

The second point of interest lies in the degenerative and hemorrhagic changes which have already taken place at this early stage of pregnancy in the decidua capsularis. These changes are limited to this area, no



Fig. 4.—Low power microphotograph showing the empty chorionic vesicle (the embryo, amnion, and yolk sac having been removed), lying in the maternal blood space and surrounded by a mantle of decidua. Note the extreme thinning of the decidua capularis. The irregularity of the surface is due to artefact.

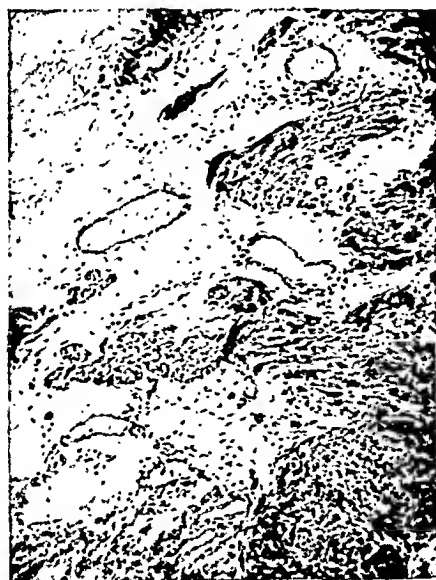


Fig. 5.—Edema of outer third of myometrium with dilatation of blood vessels. Hypertrophy of muscle cells has not as yet taken place. This change must account in part for the softening and enlargement of the uterus.

evidence of them being found in the decidua vera. It seems most likely that they are related to the stretching and distention of the thin layer of decidua separating the maternal blood space from the uterine cavity, rather than to any lack of progesterone stimulation.

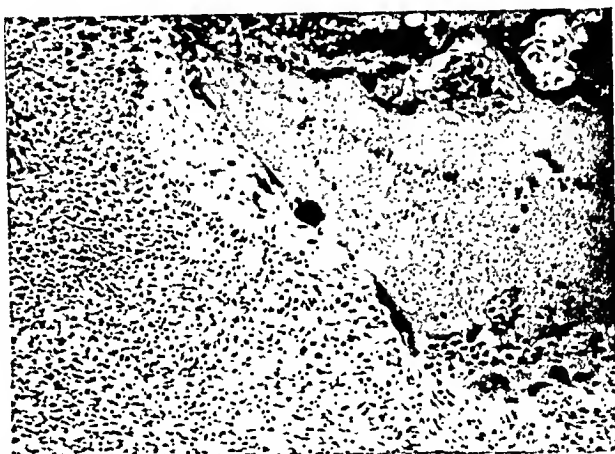


Fig. 6.—Lining of maternal blood space, showing partially broken down decidua and the beginning of a marginal layer of fibrinoid material, along the surface of which syncytial cells are arranging themselves.

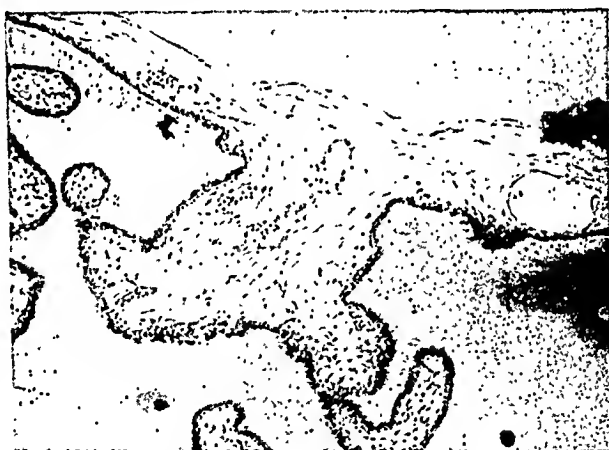


Fig. 7.—Stalk villus springing from chorionic plate and containing vessels filled with nucleated red blood cells.

Hertig and Rock have demonstrated that uterine bleeding, usually slight, but variable in quantity and duration, may announce the nidation of a uterine pregnancy. It is not difficult to imagine that these lesions may account for the bleeding which occurs not infrequently at a later period in the first trimester of pregnancies which otherwise pursue a normal course. Furthermore, it is easy to imagine the rupture of the superficial wall of the maternal blood space of an early pregnancy which is otherwise normal. Such a rupture will result in quite profuse fresh uterine hemorrhage and unless promptly sealed by thrombosis, will result in the loss of a normal pregnancy. With the presence of such lesions, trauma does not have to be considered as an additional factor. Uterine bleeding and abortions occurring in the first trimester accompanied by this characteristic bleeding may be said

to be caused by accidental hemorrhage of early pregnancy. It is particularly difficult to see what influence progesterone therapy would have on the course of this condition. The sudden bright bleeding characteristic of this type of abortion offers itself in sharp contrast to the gradual appearance of an increasing brownish uterine discharge which so often precedes the abortion of a defective ovum.



Fig. 8.—Higher magnification of decidua capularis, showing infiltrating hemorrhage and degeneration.



Fig. 9:—High power magnification of decidua capularis showing infiltrating hemorrhage.

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Discussions

DR. DONAL SHEEHAN (by invitation).—A specimen like this is of enormous importance because we are too dependent in our teaching of embryology upon chick and pig embryos. Up until a short time ago there existed only a few human embryos for study. The Peters and the Teacher-Bryce embryos turned out in the light of recent work to be abnormal, and their ages as at first estimated are no longer accepted. The Miller and the Müller embryos are each represented by only a few odd sections.

The early cleavage of the fertilized human ovum has never been seen, though we have learned a great deal about it from the monkey. At the Carnegie Institution, Dr. Streeter and his collaborators have made a careful study of the early cleavage in the monkey. During the first thirty days, the stages are presumably very close to those of the human being. On the fourth day the fertilized ovum of the monkey is merely a little ball of about sixteen cells, in the typical morular phase. On the eighth day it has become a blastocyst with a single-layered trophoblast. On the ninth day nidation begins and by the tenth day the amniotic cavity has formed, and the trophoblast has become bilaminated and lacunae have appeared. From this stage onward we can go direct to early human embryos for study. During the last three years a number of these specimens have been described. The two earliest include one described by Krafka (1942), a seven-day human embryo discovered in the tube, a fairly late ovum to be found outside the uterus, and a second embryo, to which Dr. Studdiford referred, the earliest of the Hertig-Rock collection. The latter is a seven-and-a-half-day embryo which has just started to be implanted, is not as yet covered by the epithelium of the uterus and is in the typical blastocoele phase.

I would like to bring out in the discussion the question of judging the age of such specimens of early human ova. A certain degree of accuracy can be obtained from comparison with the monkey, but there must always be a small element of doubt in this method. If, however, the age is based on the menstrual history and the estimated time of ovulation, we are on perhaps more debatable ground. Ovulation presumably takes place about the fourteenth day, but a certain amount of variation must occur in this date. And how long after ovulation does fertilization occur? It is generally believed that not more than one day elapses between ovulation and fertilization, but possibilities of variation exist. The nidation of the fertilized human ovum may start, at the earliest, on the fifth day after ovulation, but it may be any time from the fifth to the ninth day. Therefore, in judging the age of an early embryo from the menstrual history alone, one might conceivably make a mistake of one or two days which, of course, in these early stages, may be very significant.

I do not think, however, from the teaching point of view, we are so interested in the exact age as in the stage of development of the embryo, in the steps of progress which have taken place in the various organ systems. It is from this standpoint that it is so important that more of such specimens should be collected to fill out the true history of human development. You gentlemen have the opportunity to make this material, when accidentally obtained, available for study. It should be sent in a properly fixed condition, preferably, I think, to the Carnegie Institution, where facilities are available for adequate sectioning and study.

I was interested to note that Hertig and Rock had found, out of a series of twelve early ova, seven normal which were all implanted on the posterior wall,

and five abnormal which were in each case implanted on the anterior wall. I am curious to know whether Dr. Studdiford feels that there is any relationship between the state of the embryo and the site of implantation. It would seem to me that in these cases it was a matter of pure chance.

DR. WILLIAM E. STUDDIFORD.—I think that Rock's observation that all normal implantations occurred on the posterior wall and all abnormal implantations occurred on the anterior wall must be just one of those runs of figures that occur in a small series of cases. We all know that we find perfectly normal pregnancies with the placenta on the anterior wall of the uterus as so often noted in cesarean section.

THE ERGOT ALKALOIDS

A Comparison of Ergonovine With the Total Alkaloids in Their Effects on the Puerperal Uterus

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TWO groups of ergot alkaloids are known to exist; the active substances including ergonovine, ergotoxine, ergotamine; and the inactive isomers including ergometrinine, ergotinine and others. The active alkaloids may be further divided into the (1) water soluble ergonovine which has a prompt but relatively fleeting oxytocic effect upon the uterus and (2) water insoluble ergotamine-ergotoxine group with a slower but more prolonged effect. Until the last seven years it was thought that the therapeutic potency of ergot resided exclusively in the water insoluble ergotamine-ergotoxine alkaloids. However, it should be noted that some years previously certain clinical observers had commented upon the fact that occasionally one did note some oxytocic effect in the water solutions of ergot but these observations were never reported or followed up. In 1929, Thompson, then at the University of Maryland, recognized the instability of the fluid extract of ergot and subsequently advised the use of a dry alkaloid salt, ergotamine tartrate.¹

The foundation for all of our newer knowledge of ergot was laid by Chassar Moir at the University College Hospital in London, England.² Using an inflated rubber bag in the puerperal uterus he connected this by way of a rubber tube to a manometer which recorded the contractions of the uterus upon a kymograph. By the injection, separately, of the various alkaloids of ergot, he was able to demonstrate the relative therapeutic potencies of each. He concluded from these studies that both ergotamine and ergotoxine administered intramuseally will produce strong uterine contractions; however, their action when given by this route is slow, often requiring fifteen to forty-five minutes for their effect to become apparent. In the second paper³ Moir and Dale demonstrated for the first time that an aqueous extract of ergot given orally produced a marked stimulation of the puerperal uterus. They concluded that most of the oxytocic effect of ergot depended upon a yet

unidentified substance. In January, 1935, Thompson⁴ confirmed the work of Moir by experiments upon the pregnant cat. In March, 1935, Dudley and Moir⁵ reported the isolation of the truly active principle of ergot which they called ergometrine. In April of the same year, Kharasch and Legault reported independently their isolation of the same alkaloid which they called ergotoein. It should be said in passing, however, that in February, 1935, Davis, Adair, Rogers, Kharasch and Legault published a clinical report which was the basis for their laboratory report on ergotocine which followed several months later.⁶

Without doubt, this new water soluble alkaloid, now officially termed ergonovine in this country, is the most active and the most consistently potent of the ergot alkaloids. In contrast to the salts of other alkaloids such as ergotamine tartrate, it is effective when administered orally. Its prompt and consistent oxytocic action is very fleeting, however, while the slower and less dramatic effect of the ergotamine-ergotoxine group is prolonged and well sustained. The question arises as to whether in clinical practice, ergonovine should completely replace the other alkaloids of ergot or whether a combination of the short acting ergonovine with the longer acting total alkaloids should prove most desirable. Moir believes that ergonovine "has supplanted the alkaloids previously in use,"⁷ while Thompson says "there is no single constituent of ergot that is representative of the full clinical oxytocic activity of ergot."⁸ Guggisberg agrees in that he believes that the best clinical results will be obtained with a combination of ergonovine with the ergotamine-ergotoxine alkaloids.⁹

Clinical Comparison

Ergonovine and Total Alkaloids

One of the great contributions to obstetrics of the last decade came when Davis advocated the routine intravenous injection of ergonovine immediately after delivery of the fetal head. This investigator recommended the routine administration of 0.2 mg. of ergonovine maleate (Ergotrate, Lilly) as the shoulders were being delivered. He reported that immediate tonic contractions of the uterus invariably followed with early separation of the placenta and prompt expulsion. Blood loss was greatly reduced in all cases and the prompt delivery of the placenta provided a clear and dry field for the episiotomy repair. A series of other published reports soon followed confirming the good clinical results reported by Davis. After these favorable reports appeared, I adopted the routine injection according to the plan advocated by Davis and found that the average time interval in my cases between the intravenous administration of ergonovine and the delivery of the placenta was 3.1 minutes. This was the average in a consecutive series of 71 cases. Average blood loss in these patients was greatly reduced and the prompt delivery of the placenta facilitated the episiotomy repair. Although the results were far superior to any plan of oxytocic administration

previously employed, it was observed that a rather high incidence of delayed post-partum bleeding occurred. A small minority, 12 per cent in this group of 71 patients, had sufficient bleeding during the first two hours after delivery to require the second dose of ergonovine. In this bleeding group it was observed that the patient would leave the delivery room with a firm, contracted uterus only to be reported by the floor nurse on arrival in her room that the patient was bleeding and the uterus atonic. The delayed bleeding in this group was in no case alarming but this observation plus the well known fleeting action of ergonovine prompted an investigation of the short acting ergonovine in combination with the longer acting total alkaloids of ergot for intravenous injection during the placental stage of labor. An ampoule containing the total alkaloids of ergot was supplied by the manufacturer. This combination of ergonovine with the total alkaloids was given intravenously immediately after delivery of the fetal head to a consecutive series of 54 obstetric patients. The time between the injection and delivery of the placenta was carefully recorded with a stop watch and found to average 2.9 minutes. The shortest time was 30 seconds and the longest 8.5 minutes. No incarcerated placenta was encountered, and the blood loss in each patient was minimal, with the exception of one in whom the uterine response to the intravenous injection was delayed. Attempts were made to collect and measure the blood loss during and after the placental stage, but in my experience no satisfactory method of collecting the uterine blood loss has yet been devised and therefore the figures are not given. No cases in this series required a second dose of ergot for delayed bleeding within the first three hours after delivery and their uteri remained firm.

This clinical experience inspired the very definite impression that the routine use of ergonovine immediately after delivery of the fetal head provided a safe, effective, physiologic method of terminating the placental stage quickly and with minimal blood loss. It was also apparent that the short acting ergonovine, while highly satisfactory for the quick termination of the third stage, was followed within two hours of delivery by a disproportionately large group (12 per cent) of secondary uterine atonia which could be prevented by the use of ergonovine in combination with the total alkaloids of ergot instead of the ergonovine alone. In order to confirm or deny this clinical impression, a study of puerperal uterine contractions was undertaken, using an intrauterine balloon connected to a manometer.

Pharmacologic Comparison

Ergonovine and the Total Alkaloids of Ergot

Technique of Experiment.—A sterile rubber balloon of 80 c.c. capacity was inserted into the puerperal uterus within twenty-four hours after delivery. As previously reported, this is the period of maximum sensitivity of the puerperal uterus to oxytocics. The balloon was so

shaped that when distended with water its two "horns" filled the uterine cornua thereby anchoring it in place. The balloon was filled with sterile water until a distending pressure of 40 mm. was reached. This was the standard distending pressure used in all experiments as it has been learned by previous studies that this pressure is best suited for bringing out the uterine motility to a point where it can be readily recorded by the mechanical type of ink writing manometer used in these experiments.

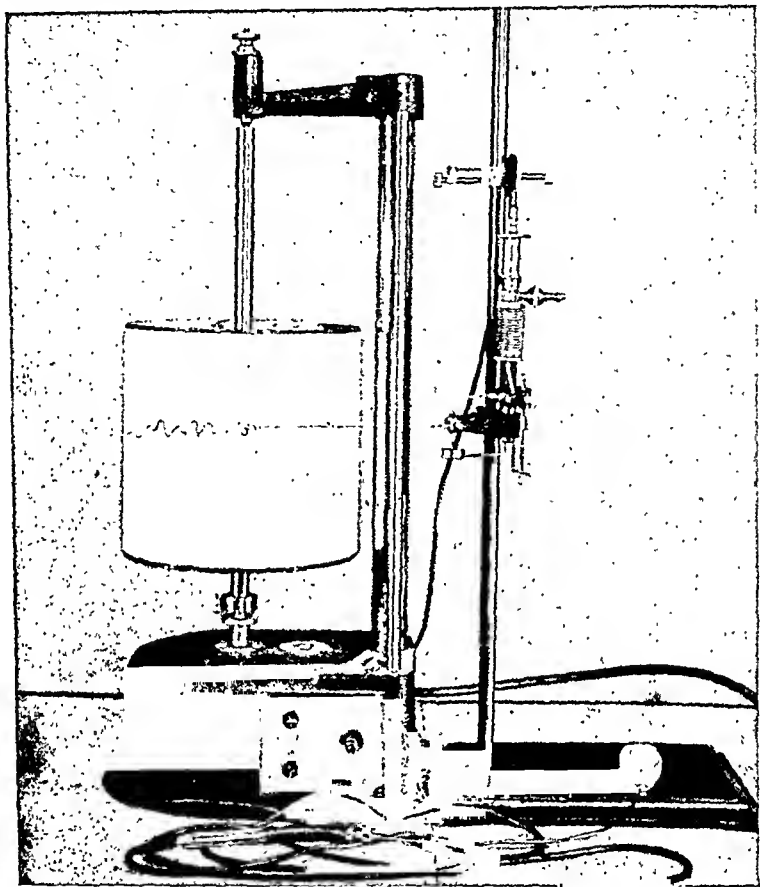


Fig. 1.

Often with lower pressures, no contractions can be recorded. It must therefore be emphatically stated that these tracings are comparative and do not necessarily represent the intrinsic motility of the puerperal uterus in the absence of a distending foreign body. The balloon is connected by way of an attached woven catheter to a rubber tube with the mechanical ink writing manometer so arranged that the contractions of the uterus are graphically recorded on the revolving kymograph. Trauma incident to the introduction of the balloon always throws the uterus into spasm which subsides within several minutes; tracings were started after the spasm had disappeared. The time intervals on the tracings were recorded by an electric timer. Injections of the solutions under investigation were made intravenously at the points indicated by the arrows, the arrow being the point at which the injection was completed. The ergonovine employed in these experiments was in each instance the 1 c.e. ampoule of ergonovine maleate (Ergotrate-Lilly) 0.2

mg. The total alkaloids employed in these experiments was in each instance the 1 c.c. ampoule of total alkaloids of ergot (S. S. Ergot Alkaloids-Upjohn). This ampoule contains 1.12 mg. of total alkaloids calculated as ergotoxine, 0.78 mg. of water insoluble alkaloids calculated as ergotoxine, and 0.183 mg. of water soluble alkaloids calculated as ergonovine. In this combination it is impossible to calculate the exact amount of ergonovine but the total water soluble alkaloids calculated as ergonovine is determined by the Hampshire-Page method of assay. Each c.c. of this solution contains approximately 0.17 mg. of ergonovine which is equivalent theoretically to 0.2 mg. of ergonovine maleate (Fig. 1).

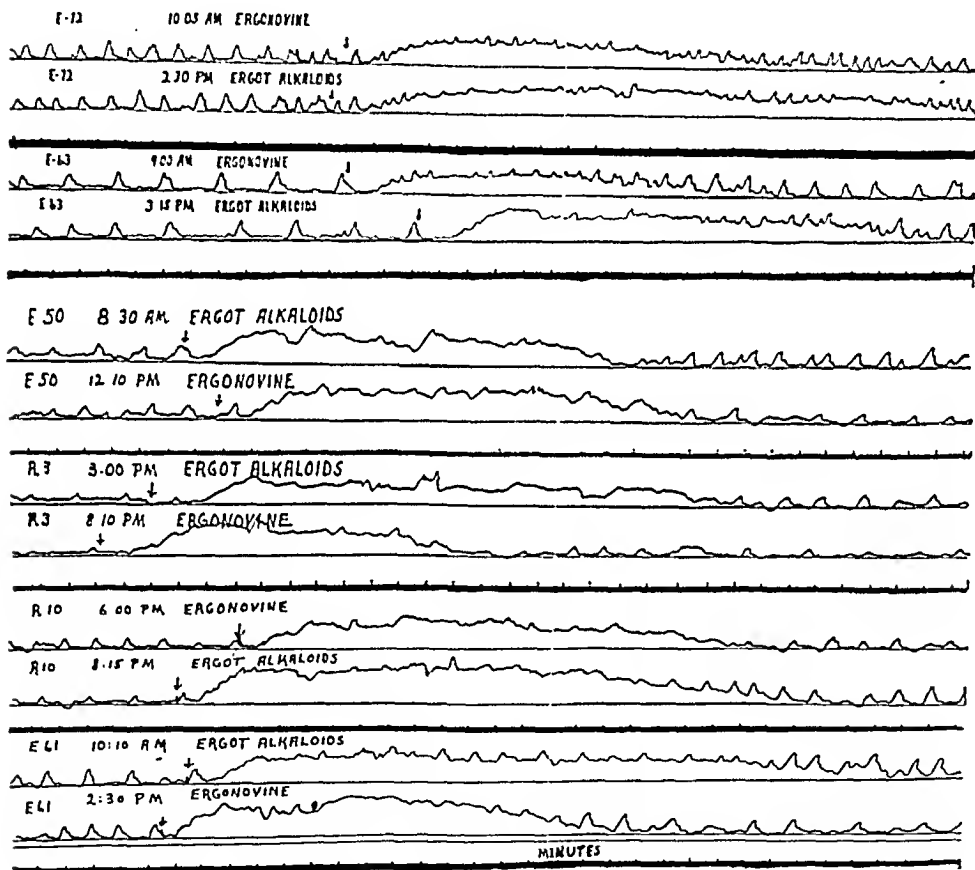


Fig. 2.—Graphs showing comparison between effects of ergonovine alone and with total alkaloids on the puerperal uterus. Case E-72, Ergonovine Effect, 12 minutes, no change in motility. Total Alkaloids Effect, 22 minutes, marked increase in motility. Case E-63, Ergonovine Effect, 12 minutes, no change in motility. Total Alkaloid Effect, 16 minutes, marked increase in motility. Case E-50, Ergonovine Effect, 16 minutes, slight stimulation to motility. Total Alkaloids Effect, 15 minutes, marked increase in motility. Case R-3, Ergonovine Effect, 12 minutes, moderate stimulation to motility. Total Alkaloids Effect, 18 minutes, marked increase in motility. Case R-10, Ergonovine Effect, 17½ minutes, no effect on motility. Total Alkaloids Effect, 22½ minutes, marked increase in motility. Case E-61, Ergonovine Effect, 15 minutes, no effect on motility. Total Alkaloids Effect, 24 minutes, marked increase in motility.

Outline of the Study.—Tracings shown in this report were obtained by the technique just described from the puerperal uteri of 12 normal primiparas delivered at term. In all of them the labors were uneventful, no sedation or other medication was given during labor and the only anesthesia employed was procaine hydrochloride pudendal nerve

block for the performance of the outlet forceps. Epinephrine was omitted from the procaine and no oxytocic was given to the patient prior to the experiments. All of the tracings were taken on the first day postpartum, usually within a few hours after delivery. The initial tracing was often taken immediately after delivery of the placenta and the second tracing on the same patient several hours later, after the effect of the first experiment had disappeared. Since the response of different uteri to oxytocics is quite variable, it was necessary to compare the effects of ergonovine alone and the total alkaloids on the same patient. Some received the ergonovine for the initial experiment, in others the procedure was reversed.

Explanation of Tracings.—Uterine contractions were recorded on the first day post partum in 12 normal primiparas. The tracings obtained on 6 of these patients are shown as fair samples of the entire group. It will be noted that each patient received one dose of ergonovine and one dose of total ergot alkaloids as previously described. The first tracing was taken usually about one hour after delivery, the effect of the intravenous injection of ergonovine or ergot alkaloids being recorded at this time. After a period of time indicated on the tracings, the ergot preparation not given at the initial experiment was given for comparison. Tonic contractions followed promptly the injection of the ergonovine or total alkaloids in every case. This marked oxytocic effect became apparent in thirty to ninety seconds in all cases and no difference in reaction time between ergonovine and the total alkaloids could be elicited. However, in the duration of the response there was a marked difference. For all of the tracings the average duration of the total alkaloid response was twenty minutes while that for ergonovine was 14 minutes. In half of the patients a prolongation of the total alkaloid effect is demonstrable and in the other half the ergonovine and total alkaloids effects are about the same. In one case was the ergonovine effect longer than the total alkaloids effect. The most consistent difference between the two was demonstrated in the pattern of uterine motility which followed the tonic response. It will be seen from the tracings that following the tonic contractions induced by the total alkaloids, there was in each case a hypermotility of the myometrium as shown by the more rapid rate and increased amplitude of the contractions. The ergonovine tracings occasionally show some tendency to this increased uterine contractility but it is not constant; it is the rule in the total alkaloid tracings.

Conclusions

1. Ergonovine, the water soluble alkaloid of ergot, has a prompt but fleeting oxytocic effect upon the puerperal uterus. Given intravenously, there is a tonic response in thirty to ninety seconds which persists on the average of 14 minutes. Following the tonic response, there is no consistent alteration in the pattern of uterine contractions from that seen before the ergonovine was given. Clinically the intravenous administration of ergonovine (0.2 mg.) just after delivery of the fetal head is followed by expulsion of the placenta in 3.1 minutes (71 cases) with minimal blood loss. Uterine atonia follows in 12 per cent of the patients, requiring a second injection of the oxytocic within two hours of delivery.

2. Total alkaloids of ergot, a combination of 0.17 mg. of ergonovine with 1.12 mg. of total alkaloids calculated as ergotoxine, 0.78 mg. of

water insoluble alkaloids calculated as ergotoxine, has a prompt and also a sustained oxytocic effect upon the puerperal uterus. Given intravenously there is a tonic response in thirty to ninety seconds which persists for the average of twenty minutes. In these experiments 50 per cent of the uteri gave a more sustained response to the total alkaloids than to ergonovine alone. In some cases the effect is almost twice that of ergonovine alone. In one case did the oxytocic response of a uterus to ergonovine alone exceed that of the total alkaloids. After the tonic response has disappeared, there is a consistent increase in the rate and amplitude of the uterine contractions which persists for about two hours.

Clinically the intravenous injection of the total alkaloids immediately after delivery of the fetal head is followed by delivery of the placenta in 2.9 minutes (54 cases) with minimal blood loss. Uterine tonus was maintained in all cases and none required a second dose of the oxytocic within two hours.

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THE VALUE OF PELVIORADIOGRAPHY IN THE MANAGEMENT OF DYSTOCIA*

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IT IS generally acknowledged that the more accurate estimation of the qualitative and quantitative capacities of the obstetric pelvis has played an important role in the decrease in the maternal and fetal morbidity and mortality which has occurred in the last decade. Obstetricians have come to realize that pelvic estimations by the ordinary methods of external and internal pelvimetry, while of some value, are not accurate indicators of the linear measurements of the pelvis and moreover fail to give a true picture of the architectural features of the pelvis which are at least as important as the measurements themselves.

Dippel and Hodges¹¹ have shown that the external conjugate is not a true guide to the length of the true conjugate. Jacobs proved that Smellie's rule of subtracting 1.5 to 2.0 cm. from the diagonal conjugate to estimate the true conjugate is accurate in only 10 per cent of the cases studied. Scadron and Rappaport¹⁶ have shown that the roentgen measurements are consistently greater than the clinical measurements and that in many cases clinically contracted pelvises were proved to be ample by x-ray pelvimetry and subsequent delivery. The superiority of roentgen pelvimetry to clinical pelvimetry is emphasized by references to the following tables which summarize a comparative study of 350 consecutive cases x-rayed 10 days before term as a routine between 1936 and 1938 (Table I). Of 257 cases in which the clinical estimation and x-ray pelvimetry agreed that the pelvis was ample, 253 were proved ample by subsequent delivery. This indicates an accuracy in such circumstances of 98.4 per cent. Forty-four cases in which the clinical and radiologic prognosis agreed that a pelvis was contracted were confirmed, and 39 proved, showing an accuracy of 88.6 per cent.

TABLE I. DIAGNOSIS VS. CLINICAL RESULTS

DIAGNOSIS	NO. OF CASES	PROVED AMPLE	PROVED CONTRACTED	PERCENTAGE CORRECTED
1. Clinic: ample	257	253	4	Clinic 98.4
X-ray: ample				X-ray 98.4
2. Clinic: contracted	30	25	5	Clinic 16.6
X-ray: ample				X-ray 83.4
3. Clinic: ample	19	5	14	Clinic 26.3
X-ray: contracted				X-ray 73.7
4. Clinic: contracted	44	5	39	Clinic 88.6
X-ray: contracted				X-ray 88.6

*Read at a meeting of the Section of Obstetrics and Gynecology, New York Academy of Medicine, Feb. 23, 1943.

If, however, a pelvis was classified clinically as contracted, and ample by pelvioradiography, as occurred in 30 instances, and subsequent events proved the pelvis ample in 25 cases, then the x-ray was correct in 83.4 per cent and the clinical judgment in only 16.6 per cent. Conversely, in the 19 cases in which the clinical examination revealed an ample pelvis but the x-ray showed a contracted pelvis, the pelvis proved contracted in 14 cases; the x-ray being 73.7 per cent correct and the clinical judgment in only 26.3 per cent. In other words when the clinical and x-ray prognosis agree, the accuracy of prognosis is highest but when they disagree the x-ray prognosis is much more to be trusted; as a matter of fact it is three times as accurate in such circumstances.

A comparative study was also made of the accuracy of diagnosis by clinical and x-ray pelvimetry. By clinical pelvimetry, if a pelvis was considered contracted this proved to be correct in only 59.1 per cent of the cases whereas if it was considered ample the prognosis was correct in 93.5 per cent (Table II).

TABLE II. ACCURACY OF DIAGNOSIS

	DIAGNOSIS	NO. OF CASES	PROVED AMPLE	PROVED CONTRACTED	PERCENTAGE CORRECT
Clinic	Contracted	74	30	44	59.1
X-ray	Contracted	63	10	53	84.1
Clinic	Ample	276	258	18	93.5
X-ray	Ample	287	278	9	97.0

By pelvioradiography if a pelvis was considered contracted, this proved to be correct in 84.1 per cent while if it were considered ample, 97.0 per cent accuracy was obtained. In other words, the diagnosis of a contracted pelvis is not as accurate as the diagnosis of an ample pelvis but the x-ray is a great aid in properly diagnosing contracted pelvises.

Material

Since 1938 we have made pelvioradiographic studies only when dystocia was anticipated before labor, or arose unexpectedly during labor. Dystocia was anticipated if the pelvimetry done in the prenatal clinic was indicative of a contracted pelvis or if the past history of a multipara led us to believe dystocia was a factor in her previous obstetrical history. Any patient with a diagonal conjugate of 11.5 cm. or less, or who showed evidence of physical or pelvic android tendencies, was also put in the expected dystocia group. This group of cases were x-rayed at term or early in labor. In those cases in which favorable clinical prognosis was made, but in which engagement failed to occur, malpresentation was evident, or labor failed to progress satisfactorily, x-rays were taken during labor and repeated if necessary. This study consists of 280 consecutive cases studied by pelvioradiography between 1938 and 1941 because of fear of dystocia, either anticipated or unexpected. We have found the procedure of pelvioradiography of great value in the management of these cases.

Method

Roentgenological Technique.—We use a combined method of pelvioradiography which includes the best features of various methods of

roentgen pelvimetry, pelvicephalometry and determination of pelvic architecture.

We take five films: a 14 by 17 anteroposterior and lateral at 30 inches. Included in the lateral is an isometric scale which is applied to the midsagittal plane according to the Thoms principle.

The anteroposterior film is studied for presentation, position, number, attitude, size and maturity of the fetus. The interspinous diameter and the circumference of the skull are measured. On the lateral view the anteroposterior diameter of the inlet and the circumference of the skull are measured. These four measurements are corrected for distortion and converted into volumetric equivalents for comparison by the Ball nomogram. In addition, the true conjugate, posterior sagittal of the midpelvis and outlet, pubotuberous diameter, and depth of the pelvic axis are determined by the Thoms isometric scale.

A pair of stereoscopic pelvic inlet films are taken with the lumbosacral angle raised, and studied in the precision stereoscope built by Dr. Myron Schwarzschild, for the determination of pelvic architecture, fetal pelvic relationships and to check the anteroposterior and greatest transverse diameter of the inlet measurements. A 45-degree angle anteroposterior film is taken for the study of the subpubic angle, side walls, sacrum, and ischial spines. We thus have a triple check on the most important diameter, the true conjugate, and a double check on all other measurements.

Prognosis

The obstetric prognosis as defined in this paper is based on what we observe in the films: on the pelvimetry, cephalopelvic relationship, pelvic architecture and fetal attitude. To arrive at the true obstetric prognosis, the obstetrician must combine the x-ray prognosis with the clinical prognosis. As far as the estimation of the pelvis is concerned the x-ray is more accurate. However, the estimation of uterine force, cervical rigidity, soft part dystocia, size of head, age and condition of the patient is entirely based on clinical experience and judgment and perhaps is as important as the pelvic factor in a great many cases.

Classification of Pelves

All pelves were classified according to their architectural features as outlined by Caldwell, Moloy, and D'Esopo⁴⁻⁸: gynecoid, android, anthropoid and platypelloid.

Classification of Radiologic Prognosis

On the bases of the pelvic size and architecture, fetal pelvic relationships and treatment recommended, all cases were classified into one of four prognostic groups as follows: good, fair, guarded and poor, on the bases of criteria listed in Table III. The treatment recommended and the outcome expected from consideration of the radiologic features alone, are included. The fetal pelvic relationship includes a consideration of the type of synclitism, the manner of engagement, the amount of flexion and the pelvic architecture. Groups A & B are normal pelves and C & D are considered contracted.

Results (Table IV)

Group A.—Consists of those cases with no disproportion and a good prognosis. Spontaneous delivery is the rule. There were 173 cases or

TABLE III

GROUP	PROG- NOSIS	A. P.	A. P. PLUS TRANS.	FETAL PELVIC RELATION	TREATMENT	OUTCOME EXPECTED
A	Good	cm. above 10.5	cm. 24	No disproportion	Labor	Spont. delivery is the rule
B	Fair	10-10.5	22-24	Borderline disp.	Test labor	Vaginal deliv- ery is usual
C	Guarded	9-10	20-22	Relative disp.	Short trial labor	Cesarean sec- tion probable
D	Poor	7.5-9.0	Below 20	Absolute disp.	Cesarean section	Cesarean sec- tion necessary

62 per cent of the entire series in this group. In other words, in more than half the cases in which dystocia was feared, the x-ray indicated a very favorable outcome with vaginal delivery. Considering that low forceps are often elective it was decided to consider them as non-operative, and to judge all other forceps, operations, cesarean sections and other vaginal maneuvers as operative. The number of cases that required operative deliveries in group A was 35 and this amounted to 20 per cent of the group; the remaining 80 per cent delivered either spontaneously or with low forceps.

There were 7 stillbirths, two of which died before delivery, one from pneumonia, the other from maternal toxemia and sepsis. The other five stillborns died of intracranial hemorrhage sustained during vaginal delivery. If these babies were delivered by section they probably would have survived; therefore we probably were wrong in five instances in advising vaginal delivery.

The five cases sectioned in this group were sectioned for extrapelvic indications: placenta previa, diabetes, pelvic tumor and two cases of breech in elderly primiparas. We gave a correct prognosis in 168 cases and a wrong one in 5 cases; a correct prognosis of 97 per cent.

Group B.—Includes cases with borderline disproportion and a fair prognosis. A test of labor is usually recommended and vaginal delivery is the rule. There were 55 cases or 19 per cent of the entire series in this group. Operative delivery was necessary in 56 per cent. Mid-forceps was the most frequent operation and was performed in almost one-third of the cases. The incidence of operative vaginal deliveries is much higher than in group A and cesarean section had to be performed in 16 per cent of the cases. Cesarean section is often necessary in this group if the baby is over 9 pounds. Nine cases required cesarean sections, all of which were low cervical sections following a test of labor. Eight of these babies weighed over 9 pounds. It is difficult to predict the weight of the baby by x-ray because the calcification doesn't change much, but the weight increases $\frac{1}{2}$ pound a week in the last month. With average sized babies the test of labor might have resulted in a vaginal delivery. The chief value of pelvioradiography in borderline cases is to indicate that a possible section should be kept in mind and not to jeopardize the possibility of performing a safe section during labor by waiting too long or by manipulation.

There was one stillborn in this group, and it was from intracranial hemorrhage during a midforceps delivery in an android pelvis. We

TABLE IV. MANNER OF DELIVERY ARRANGED ACCORDING TO PELVIC RADIOGRAPHIC PROGNOSIS

PROGNOSIS*	TOTAL	SPONT.	LOW FORCEPS	MID- FORCEPS	BREECH EXTRAC.	VERSION	CRAN- IOT.	CESA- REAN SECTION	TOTAL OPERATIVE	% OPERATIVE	TOTAL STILL- BIRTHS	WRONG PROG- NOSIS	CORRECT PROG- NOSIS	% CORRECT
A	173	75	63	14	13	2	1	5	35	20	7	5	168	97
B	55	11	13	17	3	2	0	9	31	56	1	1	54	98
C	27	2	2	4	0	0	0	19	23	85	4	0	27	100
D	25	0	0	2	1	0	0	22	25	100	3	0	25	100
Total	280	88	78	37	17	4	1	55	114	40	15	6	274	97.8

*A, good; B, fair; C, guarded; D, poor.

were therefore wrong once and correct 54 times resulting in a correct prognosis in 98 per cent.

Group C.—This was the group with a guarded prognosis. Relative disproportion was evident and a short trial of labor with early section was advised. Ten per cent or 27 cases were in this group. Twenty-three cases or 85 per cent required operative deliveries. In 19 cases a cesarean was performed. There were 4 stillborns in the 8 vaginal deliveries. One was a spontaneous premature stillbirth. The other three were due to delivery. In all 3 cases a cesarean section was considered probable and was advised after a very short trial of labor. In these three cases the advice was disregarded and difficult vaginal delivery attempted after long labor. We made the correct prognosis in all of these cases or 100 per cent.

Group D.—This consisted of those 25 cases or 9 per cent of the series who had poor prognosis, absolute disproportion, and in which an elective or immediate section was necessary. Twenty-three of the 25 cases were either android or platypelloid types. In 22 cases a successful section was performed. In the three cases in which a vaginal delivery was attempted, stillbirths resulted.

In the entire series of 280 cases a correct prognosis was given in 274 cases, or 97.8 per cent. A favorable prognosis was given in 173 cases and 166 either delivered spontaneously or by low forceps, many of which were elective or prophylactic. Of the entire series only 40 per cent required operative delivery; this indicates the conservative effect of pelvioradiography.

Anthropoid Pelvis.—The long oval pelvis, now called anthropoid, was conspicuous in this series of dystocia cases, by its rarity and by its failure to cause significant difficulty. Twenty-two cases, or 8 per cent, of the entire series were either true or mixed anthropoid types. No anthropoid case had to be given guarded or poor prognosis and the results justified our optimism; only 12 per cent were operative and these were all vaginal deliveries. No cesarean sections were necessary. There were no stillbirths and the correct prognosis was made in 100 per cent of the cases.

Gynecoid Pelvis.—The gynecoid, female or round pelvis was the most frequent type encountered in this series, but its percentage incidence was less than in our obstetrical service at large. Of the 136 gynecoid pelves, 124 were true gynecoid, and 12 gynecoid with an anthropoid tendency. The mixed group all had a good or fair prognosis and were considered with the true gynecoid for the statistics of the total gynecoid series. From Table V it can be seen that most of the gynecoid cases were classed in the groups with a good prognosis and only 11 per cent in groups with a guarded or poor prognosis. The operative incidence was 32 per cent. Three of the 12 stillborns were in this group. The incidence of stillbirths was 2.2 per cent. A wrong prognosis was made in 2 cases and a correct one in 134. We were correct in 98 per cent of our attempts in the gynecoid series. In no case of a gynecoid pelvis in which section was recommended on the basis of relative or absolute disproportion was a live baby delivered vaginally, even though out of 13 such cases, 10 had trial of labor or attempted vaginal delivery.

Android Pelvis.—The android, male or funnel pelvis in its true and mixed form made up 34 per cent of the series. Its incidence in the dystocia series is, as expected, greater than in the obstetrical service of the hospital at large. One-third of the android cases were given a

TABLE V. PROGNOSIS AND RESULTS ACCORDING TO PELVIC ARCHITECTURE

PELVIC TYPE	GENERAL INCI- DENCE %	DYSTOCIA INCI- DENCE		A *		B *		C *		D *		OPERATED		STILBORN		CORRECTED STILLBORN STATISTICS		WRONG PROG- NOSIS	CORRECT PROG- NOSIS	% CORRECT
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%			
Anthropoid	17	22	8	25	96	1	4	0	0	0	0	3	12	0	0	0	0	0	22	100
Gynecoid	56	136	49	107	78	16	11	11	8	2	3	53	32	5	3.6	3	2.2	2	134	98.5
Platyphelloid	5	26	9	7	32	7	32	1	4	7	32	9	41	1	4.0	0	0	0	26	100
Android	22	96	34	34	35	31	32	15	16	16	17	49	51	9	9.3	9	9.3	4	92	96.0
Total		280	100	173	62	55	19	27	10	25	9	114	40	15	5.3	12	4.3	6	274	97.9

*A, good; B, fair; C, guarded; D, poor.

guarded or poor prognosis and operative deliveries were necessary in 51 per cent of the cases. In four cases in which a favorable prognosis was given stillborn vaginal deliveries resulted. A correct prognosis was given in 96 per cent of the android series. The highest incidence of stillbirths (9.3 per cent) occurred in this series.

A comparison of the true android, to the mixed android pelvis failed to influence either the prognosis or the ease of parturition to any large extent; consequently all android pelvises were classified together in this series.

Platypelloid Pelvis.—The flat pelvis occurred in 9 per cent of the dystocia series. This is about twice as frequent as in the hospital obstetrical service at large. Of the 26 cases classified as platypelloid, one-third were given a poor or guarded prognosis. The operative incidence was 41 per cent or 9 cases, all except one of which were cesarean sections. This confirms our previous impression: that if a flat pelvis is to give trouble it usually will do so early, and will interfere with engagement and necessitate an early section; however, if it fails to give trouble at the inlet it is rare that it will cause subsequent serious difficulty. The only stillbirth in this group was a spontaneous premature delivery which was due to extrapelvic cause (Table V). It is relatively easy to prognosticate this group and we were correct in all twenty-two cases or 100 per cent.

Stillbirths

In this series of 280 cases of dystocia there were 15 stillbirths, an incidence of 5.3 per cent. This is slightly above the usual hospital figure, but is not high for a dystocia series. Three of the babies died of conditions unrelated to delivery, namely, maternal sepsis and toxemia, pneumonia, and prematurity. Of the other 12 cases cesarean section was advised in 6 but this advice was disregarded and difficult vaginal deliveries resulted in stillbirths. The other six were advised to have vaginal deliveries but suffered the same fate. These are our six mistakes. The methods of delivery of the 15 stillbirths were as follows: low forceps 3, midforceps 7, breech extraction 3, craniotomy 1, and spontaneous 1.

No correction is made for the fact that soft part dystocia, poor uterine force or lack of skill played a part in these mistakes, but in some cases they were undoubtedly operative.

Choice of Forceps

In most cases ordinary pelvic curved forceps such as the Simpson, Elliott, solid blade and Williamson modifications were used. The Kielland forceps were used seven times. Two stillbirths occurred during attempts at rotation at the level of arrest in android pelvises. Possibly the choice of Barton or Kielland forceps with extraction to the outlet before rotation would have given better results, because it has been shown that the maneuver to be used in cases of arrest varies with the pelvic architecture involved; and that in flat and android pelvises only low rotation is safe.

Cesarean Section

Cesarean was resorted to 55 times or in 19 per cent of the cases in this dystocia series. This is twelve times as high as the usual incidences in our hospital in general, but is not high for a series of dystocia cases.

In those cases with a good prognosis, section was done five times, all for extrapelvic indications. In the borderline group with a fair prognosis there were 9 sections, all performed after a trial of labor failed to produce sufficient progress. In almost all of these the baby was of large size. In 27 cases with relative disproportion there were 19 sections although it was advised in 4 additional cases. In the 25 cases of absolute disproportion for all of which a section was recommended, failure to perform it in three cases resulted in three stillbirths.

Forty-four per cent of the cesareans were in gynecoid pelvis, 43 per cent in android and 13 per cent in platypelloid. There were none required in the anthropoid group.

Maternal Morbidity and Mortality

Aside from a number of cases of self-limited puerperal infection, the only significant morbidity resulted from a difficult forceps operation. This was a case of a patient with a true android pelvis and absolute disproportion for which a section was recommended. This advice was not followed and the midforceps operation with solid blades, Williamson and Barton forceps resulted in a vesicovaginal fistula and stillbirth.

There was no maternal mortality in this series.

Summary

A series of 280 obstetric cases in which dystocia was expected were studied by pelvioradiography as an aid in determining the obstetrical prognosis and treatment. The cases were classified in four groups: no disproportion, borderline, relative, and absolute disproportion; and the prognosis was good, fair, guarded and poor, respectively. Treatment recommended was based on the above considerations.

1. The roentgen prognosis was correct in 97.9 per cent.
2. As the prognosis became worse the incidence of operative deliveries increased.
3. Cesarean section was necessary for good results when poor prognosis was given by x-ray pelvimetry.
4. In 52 cases in which cesarean was considered likely, it was performed in 41 and should have been performed in 7 more as indicated by disastrous results following vaginal delivery.
5. The conservative influence of pelvioradiography in a dystocia series was shown by the fact that only 114 or 40 per cent required operative delivery.
6. The android and platypelloid pelvises were frequently found among the cases in which poor prognosis was given.
7. The anthropoid pelvises were all given a favorable prognosis, and subsequent events proved this confidence justified.
8. The gynecoid pelvis was the most difficult to evaluate correctly and the size of the pelvis was often the chief guide. There was an increase in operative deliveries in the following order: anthropoid, gynecoid, platypelloid and android.
9. Half of the stillbirths could have been avoided if the radiologic advice had been followed.
10. The cesarean operation was more accurately limited to those cases in which it was essential.

Conclusion

A correct obstetrical prognosis based on pelvioradiography was possible in 97.9 per cent of a series of cases in which dystocia was expected. Since correct treatment depends on accurate diagnosis and prognosis we feel that pelvioradiography is of great value in the management of dystocia.

LT. Emanuel Dickler, U. S. Army, former resident in radiology at Beth Israel Hospital, New York City, rendered invaluable aid in reading some of these films. Drs. I. Seth Hirsch and Arthur Bendiek, chiefs of the department of radiology at Beth Israel, were helpful in prognosticating some of the doubtful cases. Dr. Murray Resnick, resident in radiology, supervised the technical features of the pelvimetry.

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THE TREATMENT OF SYPHILIS IN PREGNANCY BY THE FIVE-DAY MASSIVE DOSE METHOD*

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THE treatment of early syphilis by the method of Hyman, Chargin and Leifer¹ in which massive doses of mapharsen are administered by continuous intravenous drip was begun as a clinical experiment at the Cook County Hospital in August, 1940.

Early in our study an unusual opportunity to observe the effects of massive dose therapy on both mother and fetus in utero occurred when a young primipara in beginning labor was found to have a syphilitic chancre on the labium. Treatment was instituted immediately and the patient had received two complete days of treatment with a total dosage of 0.48 Gm. of mapharsen when she was delivered of a full-term, normal infant. The third-day-treatment was resumed the next morning and was continued through until the end of the five-day period with no ill effects.

Shortly thereafter a young woman in her seventh month of pregnancy reported to the clinic with an eruption of secondary syphilis. She, too, was given the prescribed course and at the end of the five-day period had received the full dose of 1,200 mg. of mapharsen. Two months later she was delivered of a full-term, normal infant who is now 21 months old, in good health and free so far of any evidence of syphilis.

Encouraged by the results in these two cases, the method was then applied to other cases of pregnancy complicated by syphilis and to date, the five-day treatment has been administered to twenty-seven pregnant women, four of whom had primary lesions, fifteen eruptions of secondary syphilis, and eight latent syphilis of less than four years' duration. The majority of these patients were in the fifth month of pregnancy or later, and none of them had received any previous antisyphilitic treatment.

Technique

At the Cook County Hospital up to January, 1943, 481 cases of early syphilis in both men and women have been studied, 421 of whom have been treated by the massive dose method. In the beginning of the study the technique of Hyman et al. was adhered to carefully: a daily dose of 240 mg. of mapharsen dissolved in 2,000 c.c. of five per cent glucose solution administered by intravenous drip on each of five consecutive days. At the end of the first year of the study, it was observed that the best results were obtained in patients who had reported for treat-

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ment very early in the course of their infections; and that the failures, though few, that had occurred were all in patients who had been treated for secondary-stage eruptions. The treatment was then modified in an effort to reduce this incidence of failures. Thereafter patients with secondary syphilis were given, in addition to the mapharsen, a daily intramuscular injection of two c.c. of soluble sodium bismuth tartrate, each dose representing 22 mg. of metallic bismuth. Of the group herein reported, seventeen of the pregnancy cases have been treated by this modified method.

Results

One of the twenty-seven patients treated was lost from our observation. In the twenty-six others the pregnancy has terminated with the birth of a full-term, apparently normal infant in every case with but one exception; and in that case there was reason to believe that the mother, after having been treated successfully for secondary-stage syphilis in her fifth month of pregnancy, had then been reinfected or superinfected at a time most unfortunate for the infant. The record was as follows:

MOTHER	INFANT
11/ 1/41 Secondary syphilis	Cord blood negative
Pregnant five months	Kahn quantitative 3 units
Five-day treatment with arsenic-bismuth	3/ 9/42 Roentgenogram of long bones normal
Kahn quantitative 20 units	3/16/42 Kahn quantitative 3 units
11/ 8/41 Kahn quantitative 20 units	3/20/42 Kahn quantitative 1 unit
11/13/41 Kahn quantitative 4 units	3/25/42 Roentgenographic changes which pediatricians thought were syphilitic; radiologists thought they were not syphilitic
11/27/41 Kahn quantitative 1 unit	3/31/42 Blood test negative
12/ 4/41 Kahn quantitative negative	4/ 7/42 Blood test negative
12/11/41 Kahn quantitative negative	4/16/42 Blood test negative
In this period Dec. 4 to Dec. 11, she was exposed on several occasions to a man undergoing routine treatment for early syphilis at another clinic.	5/ 5/42 Kahn quantitative 3 units
January, 1942. Failed to report for examination	6/26/42 Kahn quantitative 560 units
2/ 9/42 Kahn quantitative 40 units	
2/27/42 Was delivered of a full-term infant	
3/ 5/42 Kahn quantitative 120 units	

Incidentally, the mother had apparently acquired both of her infections from the same man. He had been receiving the conventional syringe method of treatment but had been irregular in attendance.

Besides this group of twenty-seven pregnant patients with manifestations of syphilis, there were five others who had been treated for early syphilis by the five-day method and subsequently became pregnant. Each one had attained seronegativity. Though they received no further antisymphilitic treatment during their pregnancies, five have already been delivered of normal infants, one case 20 months after completion of antisymphilitic treatment, another 17 months, a third 11 months, the fourth 3 months and the last 10 months later.

At birth serologic tests of the cord blood were made routinely. There were four cases in which positive reactions were obtained, three of which reverted to negative within a period of two months, the other requiring four months and all have remained negative during the several months that they have been followed. In twelve other cases the mothers' blood, although indicating a diminishing quantitative titre, still gave positive

reactions at the time of the birth while the cord blood of their infants gave negative reactions. One unusual situation arose in which a fetus received two courses of treatment while in utero with no ill effects. The mother had been treated for secondary syphilis when in her second month of pregnancy, and six months later, when in the eighth month of pregnancy, she received a second course of five-day treatment because of a serologic relapse. In each course of treatment the full dosage of 1,200 mg. of mapharsen was administered. The pregnancy terminated with the birth of a full-term, normal baby.

All of the eight patients with latent syphilis who received the massive dose treatment have been delivered of apparently normal infants. It is of interest to note that five of these women gave histories of previous pregnancies, in one instance of two, and the pregnancies of all had terminated in miscarriages or abortion. None of the patients with latent syphilis had received previous antisyphilitic treatment.

Thus it would seem that the efficacy of the five-day massive dose method of therapy for syphilis in pregnant women is attested to by the fact that normal infants were born in 25 of the 26 pregnancies. The one syphilitic infant was probably the result of a new infection acquired by the mother before the infant was born. The results were the same regardless of whether the mother had primary, secondary or early latent syphilis; and the stage of the pregnancy did not influence the outcome.

The results in this group of cases would seem to indicate also that the pregnancy had no special influence upon the course of the mothers' syphilis for the results from the massive treatment were similar to those obtained in nonpregnant persons. Of the twenty-seven cases, ten have already attained seronegativity; in nine cases serologic tests show the quantitative titre to be steadily decreasing; two cases resulted in serologic relapse, an incidence of about seven per cent thus far; and in two others there was evidence to suggest reinfection or superinfection. In four others, the trend of the serologic reaction cannot yet be determined. Of the eight patients with latent syphilis, two have attained seronegativity, one of them seven months after therapy, the other 11 months later. In one the serologic titre is steadily decreasing, and in the other five, the serologic reactions have thus far been unaffected.

The treatment-reactions observed in the pregnant women were similar to those observed in nonpregnant individuals. They consisted of slight fever, nausea, headache, pain in the arm and some dizziness. Transitory albuminuria was observed in about one-third of the cases. Numbness and tingling of the feet that was persistent to the point of being annoying developed in one patient. There were no cases, however, in which serious reactions occurred.

Summary

Twenty-seven pregnant women with syphilis were treated by the five-day massive dose method of chemotherapy. In the majority of these cases a modified technique was used in which both arsenic and bismuth were administered concurrently during the five-day period. The treatment was well tolerated by both mother and fetus regardless of the stage of the pregnancy or the duration of the syphilis, whether primary, secondary or latent. In no instance was there encountered a severe reaction or interference with the pregnancy.

Of the twenty-seven cases, one was lost from observation; twenty-five have resulted in the birth of full-term, normal infants; and one syphilitic infant was born of a mother who apparently had acquired a second infection while the infant was still in utero. In addition to this group, five other patients who had been treated for early syphilis by the massive dose method later became pregnant and gave birth to normally developed seronegative infants although further antisyphilitic treatment was purposely withheld from the mothers.

The results of the treatment upon the mothers' syphilis were similar to results obtained in nonpregnant patients treated by the same method for similar types of syphilis.

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Discussion

DR. I. MICHAEL LEVIN.—I have observed twenty-six infants born of these women. Two were syphilitic and twenty-four were free of clinical, roentgenologic and serologic evidence of congenital syphilis. In the majority of instances the infants were hospitalized and weekly serologic studies were conducted for eight weeks and monthly thereafter.

One cause of confusion in the interpretation of the roentgen films was the presence of dense bands of calcification in the subepiphyseal zones. Dr. Rattner's remarks with reference to large doses of soluble bismuth being administered to the mothers may explain this picture.

On our service in the children's division of the Cook County Hospital, we have now treated about seventy-five infants with congenital syphilis by a method closely related to that described by the essayist. Radical changes in treatment had to be worked out because we were dealing with syphilis in a later and more widespread stage and with infants whose nutritional and growth requirements had to be met. Our experience with early acquired syphilis has been very successful and we are encouraged with our studies over the past three years with congenital syphilis.

The five-day treatment of early syphilis in pregnancy is entirely feasible, and offers the hope of a short, decisive control of syphilis, with the birth of normal children.

DR. BERTHA M. SHAFER.—In the survey made in Chicago, in 1937, we found that of 615 pregnant women who were infected with syphilis less than 50 per cent had been diagnosed as having syphilis before the fifth month of their pregnancy. We are agreed that if we are to have a good prognosis we must start our treatment before the fifth month. Not only must we start the treatment by that date, but we must carry on an intensive type of treatment with a high degree of regularity during the remainder of the pregnancy.

This evidently involves a hardship to many mothers, a fact proven quite conclusively by the observation that only 21 per cent of the women studied carried through with the treatment outlined for them. If the rapid five-day intensive treatment gives us better control over these patients, we should consider this point a definite advantage for this form of treatment.

Some believe that this rapid form of treatment does not sterilize open lesions very much more rapidly than two or three injections of arsphenamine might do.

It is true, if we compare the intensive form of treatment with the more conservative type, we cannot yet prove conclusively that we will not have more relapses. Syphilis has to be watched over a long period of time before we can speak of cure. Knowing they can be cured in five days may make these patients consider their infection is not too serious. I am sure we are going to have much difficulty in keeping a large percentage of these patients under observation long enough to prove the value of the treatment.

Let us consider the difficulties in enforcing completion of the older form of treatment. In the 1937 survey of the 11,400 patients that we studied, we found only 3,290 had had any previous treatment up to the time they came into the clinic. Since the disease was of more than four years' duration a little more than 72 per cent of these patients had suffered from it for four years without any treatment. Only 6 per cent of the women who had taken treatment had taken the minimal amount. Hence, you see how far from ideal were the conditions surrounding the other form of treatment.

My special interest in these pregnant women, concerns primarily the epidemiology of these cases. The results have been most revealing. The case of reinfection reported by Dr. Rattner is an outstanding example of the need of rendering all cases noninfectious. We know that her source of infection had been diagnosed as a primary case in August while she came into the hospital in November with secondary syphilis. The boy who was the source of the trouble did not follow through with the treatment, even though he had been urged to take intensive therapy at that time. In January, she had been made negative by treatment but she was then reinfected by this boy. We were also able to trace seven other primary and secondary cases which had resulted from this one case that had refused to have the intensive form of treatment. The epidemiology in syphilis is limited only by your time and energy.

THE USE OF VAGINAL TAMPONS FOR THE ABSORPTION OF MENSTRUAL DISCHARGES*

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DURING the recent years the use of vaginal tampons for the absorption of the menstrual discharges has increased greatly. Many patients using tampons for that purpose have inquired as to whether or not such a practice was harmful. Many gynecologists have expressed opinions on the subject, but there is little accurate information in the medical literature. This study was undertaken to determine if the use of self tamponage for the absorption of the menstrual discharges was harmful.

*This study was aided by a grant from the International Cellucotton Company, Chicago, Illinois.

Historical

The use of tampons in the vagina is not an innovation. In 1776, Leroux, a French physician in Paris, reported the use of vaginal tampons. He used a piece of tightly wound linen cloth dipped in vinegar, inserting it into the vagina to control hemorrhage and to treat leucorrhea. In 1806, Wendellstaedt, a German physician, used a tightly wound piece of linen cloth dipped in copper sulfate solution for the treatment of vaginal discharge and to stop hemorrhage. In 1888 Dührssen introduced the use of iodoform gauze as a tampon for vaginal antisepsis.

When packs of cotton, wool, gauze or rubber balloons are inserted into the vagina, nose, ear, or rectum, they are called tampons. Tampons of varying size, made of cotton or wool with a short string attached so that they may be removed from the vagina by the patient after a specified time, have been used by the medical profession since 1888 for the topical application of antiseptics or for the drying of the vagina. Long before our time theatrical performers and professional models used tampons in the vagina to absorb the menstrual discharges. The vagina was filled with absorbent cotton for this purpose.

On Sept. 12, 1933, a type of vaginal tampon for the absorption of the menstrual discharges was patented by E. C. Haas of Denver, Colorado, and, shortly thereafter, was sold by department and drug stores for that purpose. They became very popular about 1936 when an extensive advertising campaign was launched by the manufacturers. It was at about this same time that patients who were using these tampons began to ask physicians whether they were safe to use and whether the medical profession recommended their use. Since little, if anything, was known concerning the safety of their use, it was difficult to answer these questions intelligently.

Arnold and Hagele,¹ in 1938, reported an investigation which determined the efficiency of tampons in collecting the catamenial discharge of normal women. They suggested that, 'since tampons are foreign bodies in the vagina and since it is not known from experience how susceptible the vaginal mucosa might be to repeated irritation, periodic examination of the vagina should be made.

Much correspondence appeared in the *British Medical Journal*² in 1938 and 1939, some writers recommending the use of tampons and others condemning their use.

In 1939, Sackren³ reported a study of 21 subjects who were observed over a period of three to five months' use of vaginal tampons for the absorption of the menstrual discharges. He concluded that the tampons used (1) offered complete protection to 90 per cent of the women observed and in 94 per cent of the menstrual periods studied; (2) showed no tendency to block the flow; (3) produced no observable changes in the vaginal or cervical tissues (no irritation); (4) caused no infections; (5) were easy and comfortable to use and eliminated odor; and (6) were favorably regarded by the patient.

In 1939, Genell and Lysander⁴ reported three cases of colpitis which they attributed to the use of menstrual tampons. They regarded them as an unhygienic method of absorption of menstrual blood and did not recommend their employment as a substitute for perineal pads.

In 1939 a questionnaire was circulated among a group of American gynecologists asking them: (1) whether vaginal tampons furnished complete protection during the menstrual cycle; (2) whether vaginal tampons were free from all hazards of irritation, discomfort, introduction of infection, and arousing erotic tendencies; (3) whether tamponage prevented or eliminated menstrual odor. The majority of those who answered the questionnaire did not favor the use of vaginal tampons during the menstrual period, giving as reasons: (1) danger of infection, and (2) damming back of menstrual blood.

Since there was no accurate information available of studies carried on over any considerable period of time indicating whether or not the use of self-tamponage for the absorption of menstrual discharge was harmful, it was decided to undertake such a study.

Plan of Study

A group of 100 women between the ages of 19 years and 40 years volunteered as subjects for the study. They reported for an initial pelvic examination before starting the use of the tampons in November, 1939. At the time of this first examination a detailed menstrual history was obtained and the subject was instructed in the use of the tampon. Instructions to each subject were as follows: (1) Use the tampon throughout each menstrual period; (2) change the tampon at least every three hours during the time of the most profuse flow; and (3) observe carefully the following: (1) duration of the period; (2) are the tampons comfortable to insert; (3) are you conscious of the tampon while wearing it; (4) do you feel safe in wearing the tampon alone throughout each period; (5) does the tampon stay in place; (6) do you have any difficulty in removing the tampon; (7) is there any gush of blood following the removal of the tampon; (8) is there any vaginal discharge or any increase in vaginal discharge following the use of the tampon; (9) is there any pressure on the rectum or bladder by the tampon?

Tampons and vulvar pads to be used for each menstrual period were supplied to each subject throughout the period of study. Subjects were permitted free choice of one of five tampons which were available at the time this study was started. After the first examination each subject reported at intervals of every two months for an interview and a pelvic examination. All data obtained were recorded on special data cards. The study was completed in January, 1942.

The original plan had been to continue the study for a period of one year. As work progressed it seemed advisable to continue the observation over a longer period of time. Therefore, the study was extended over a period of another year, a total of 24 months.

From time to time during the two-year period subjects were lost from the group because of accepting employment in distant communities, illness, or pregnancy. At the end of the first year of study, eighty of

the original 100 subjects remained in the group to continue for another year. To this were added 23 new subjects. When the study was completed, 56 subjects had reported for 12 examinations, 30 subjects had reported for 6 examinations, and 24 subjects had reported for a varying number of examinations in excess of six (Table I). The 13 subjects who reported for less than 6 pelvic examinations; i.e., less than one year's period of observation have not been included in this analysis. Therefore, the observations which follow were made on 110 subjects who used vaginal tampons for the absorption of the menstrual discharge over a period of no less than twelve months and no longer than twenty-four months. During this period of time a pelvic examination was done on each subject every two months.

TABLE I

NUMBER OF SUBJECTS	MONTHS OF OBSERVATION	NUMBER OF EXAMINATIONS
56	24	12
6	22	11
8	20	10
3	18	9
4	16	8
3	14	7
30	12	6

Analysis of Results

All of the subjects were active young women between the ages of 19 and 40 years who were either students or career women; 14 members of the group were married and 96 members were single. Many in the group (63) had used vaginal tampons during menstrual periods for varying periods of time before becoming a member of this group. Forty-seven subjects had never used vaginal tampons before joining the group under study. Two members of the group had used tampons regularly for three years, two members had used them for two years, and the other 59 members of the group had been using them for times varying from one month to 18 months. It is interesting to note that one of the members of the group had used vaginal tamponage daily over a period of eighteen months because of leucorrheal discharge.

There was very little complaint of any discomfort experienced on introducing the tampon into the vagina. Twelve subjects stated that they had some discomfort on insertion of the tampon during the first menstrual period for which tampons were used. These were subjects who had never used tampons before. Those tampons encased in a cardboard tube were preferred by the subjects as they stated that they were more comfortable to insert.

The protection afforded by the use of the tampon was complete in 38 subjects, or 34.5 per cent. Protection was considered as complete only if the subject was able to use and felt quite safe in using the tampon alone without the additional protection of a vulval pad, throughout the entire menstrual period. Seventy-two of the subjects, or 65.5 per cent, found it necessary to use vulval pads in addition to the tampon during the period of maximum flow. Many of these subjects stated that they felt that the string attached to the tampon to facilitate its removal from the vagina acted as a "wiek" thus making it necessary to wear a vulval pad for safety in protection.

Since this study was undertaken to determine, primarily, whether there were any harmful effects produced by the tampon, care was taken to record any pelvic pathology present at the time of the initial examination and to observe closely any change which occurred in this pathology during the period of observation. Throughout the study careful notation was made of any pathologic change which occurred. Vaginal smears and a hanging drop preparation of vaginal discharge were repeated at the time of the sixth, ninth, and twelfth pelvic examinations. It is to be regretted that these smears were not taken at the time of the first examination.

The one pathologic condition which was found most frequently was that of cervical erosion. Fifty-one of the 110 subjects showed some degree of cervical erosion. In 13 of these subjects the lesion was severe, extending over an area of approximately 1 cm. radiation from the external os, being very red and granular in appearance and having a tendency to bleed when wiped with a cotton pledget. Seven subjects had moderate cervical erosion in which the lesion extended for no more than 5 mm. radiation about the external os and did not bleed when wiped with a cotton pledget. Slight cervical erosion characterized by slight reddening and a granular appearance of the cervical mucosa extending 1 to 2 mm. about the external os was present in 31 subjects.

The other pathologic conditions occurred with much less frequency. Twenty-four subjects had a retroversion of the uterus. Three subjects had intramural fibromyomas of the uterus. Ovarian pathology was present in 17 subjects. Five subjects had a unilateral ovarian cyst present at the time of the first examination. Of the other 12 subjects with ovarian pathology, 9 had palpable enlargement of one ovary only and 3 had palpable enlargement of both ovaries. One subject had a cystocele and a rectocele. Fourteen subjects had a profuse purulent discharge, and 6 had a moderate purulent discharge present at the time of the first examination. This was invariably associated with the presence of a severe or moderate cervical erosion. A caseous discharge was present in 2 subjects. Twenty-five subjects had a moderate increase in the normal mucoid vaginal secretion.

Gynecologic surgery was done on three of the subjects who had a unilateral ovarian cyst because the patients were having symptoms which interfered with their performance of daily duties. Two of the subjects had a unilateral oophorectomy. The third subject had an oophorectomy and a supravaginal hysterectomy. No attempt was made during the period of observation of these subjects to correct cervical erosion or any pelvic pathology other than that described above. This was done deliberately so that one could evaluate more accurately any changes which might be caused by the tampon; i.e., increase in existing pathology.

At the conclusion of the period of study, i.e., twenty-four months after the first examination was made, 50 of the 110 subjects (or 45.5 per cent) showed no change in pelvic findings. In the 60 subjects in whom some changes were observed, the greatest change was in those of the 51 subjects in whom cervical erosion had been present at the initial examination. Fourteen had no cervical erosion and 17 showed less erosion at the end of the period of study. The cervical erosion was unchanged in the other 20 subjects. There was no increase in severity of the erosion in any case nor did any cervical erosion develop in a subject who had not had the lesion at her initial examination. Leucorrheal dis-

charge was less in the 20 subjects showing moderate to profuse purulent discharge. One subject, who had no increased leucorrhœal discharge, had a moderate amount of mucoid discharge present at the end of the study. In one of the three subjects with fibromyoma uteri there was slight increase in the size of the tumor.

The incidence of infection with *Trichomonas vaginalis* and *Monilia albicans* was low in this group of subjects. Four subjects, or 3.63 per cent, had *Trichomonas vaginalis* organisms present in the vaginal secretion. Reported percentages of the incidence of *Trichomonas vaginalis* infection vary from 4 per cent to 69.9 per cent. Four subjects (3.63 per cent) had *Monilia albicans* present in the vaginal discharge. No other infections were present at the first examination or occurred during the period of study.

The following subjective information was obtained from the routine interrogation of each subject at the time of each examination: (1) 12 subjects reported some discomfort on inserting the tampon during the first menstrual period for which they used, (2) none of the subjects had any difficulty in removing the tampons, (3) 6 subjects noted a gush of blood following the removal of tampon on one occasion only; 2 subjects noted an occasional gush of blood following the removal of tampons. These subjects had a profuse menstrual flow; (4) 51 subjects noted an occasional increase in leucorrhœal discharge; (5) 27 subjects noted occasional pressure on the rectum or bladder by the tampon (this occurring when the tampon had not been inserted high enough in the vaginal vault); (6) 92 subjects stated that they would continue to use tampons throughout the entire menstrual period, 11 subjects stated that they would use them during the last days of the period, only, when protection was complete; (7) one subject, only, stated that she felt that the use of the tampon caused an increase in dysmenorrhea. In no other instance did a subject state that the tampon had caused or had increased an existing dysmenorrhea; (8) 60 subjects stated that the use of the vaginal tampon had decreased or eliminated entirely the odor of the menstrual discharge. Twenty-six subjects stated that they had never noted any odor of the menstrual discharge.

Summary

One hundred and ten subjects using vaginal tampons for the absorption of the menstrual flow throughout each period were interviewed and examined every two months over periods of time varying from a minimum of one year (30 subjects) to a maximum of two years (56 subjects).

There was no evidence of any irritation of the cervix or vagina by the tampon.

There were 3.63 per cent of the subjects who had *Trichomonas vaginalis* organisms in the vaginal discharge. (This incidence of infection is lower than the average given in most statistical studies of groups of 100.)

There were 3.63 per cent of the subjects who had *Monilia albicans* present in the vaginal discharge.

No subjects acquired trichomonas or yeast infections during the period of study. There was no evidence of any other pelvic infection during this period.

There was no evidence that the use of the tampon caused obstruction to the menstrual flow.

Because of the greater comfort experienced, 103 subjects preferred to continue to use the tampons through part or all of the menstrual period rather than to return to the use of the perineal pad alone.

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EFFECT OF PREGNANCY ON THE MINERAL CONTENT OF DENTIN OF HUMAN TEETH*

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IT IS commonly believed that pregnant women have more dental caries than other individuals,¹ and that this supposed increase in caries during pregnancy is caused by demineralization of the teeth. The belief is that calcification of the fetus depletes the maternal stores of calcifying minerals to such an extent that even the mother's teeth are demineralized and hence are more susceptible to caries.

Clinical studies have shown that neither the extent of caries,² nor the incidence of new cavities,²⁻⁴ is any greater in groups of pregnant women than in nonpregnant controls of the same age. Nevertheless pregnant women do have dental caries. If this caries is associated with metabolic demineralization of the teeth, one would expect the dentin to have a lower mineral content during the latter months of pregnancy than at other times. Although it has been concluded from clinical x-rays of the teeth in hyperparathyroidism that teeth do *not* take part in generalized decalcification,⁵ no adequate chemical analyses can be found to support the idea that they may not be demineralized during pregnancy.

In order to test this possibility, the average mineral content of dentin from teeth extracted after the fifth month of gestation was compared with that of other teeth selected at random from nonpregnant subjects. Dentin was analyzed because it was felt that any change in the mineral content of this tissue would be greater than the relatively inert enamel. The method employed is based on the principle that the mineral content of enamel⁶ or dentin⁷ is proportional to its specific gravity. Specific gravity determinations were made on blocks of the noncarious portions of the dentin.

*Delivered at the University of Pennsylvania School of Dentistry, Philadelphia, Pennsylvania.

Experimental

Twenty-nine carious teeth, extracted from twenty patients during the latter months of pregnancy, were collected and preserved in 3 per cent formalin solution. Longitudinal sections were cut from them and ground planoparallel, approximately 0.5 millimeter in thickness. Blocks were then cut from the noncarious portions of the dentin and the specific gravity of each was determined by flotation in mixtures of bromoform and petroleum ether.

Results

Table I shows the average specific gravity of 152 samples of dentin from the pregnant group to be 2.12 with a range from 2.03 to 2.21. Apparently there is no progressive decrease in specific gravity from the fifth to the ninth month, either in the crown or root, as would be expected if decalcification were taking place.

Discussion

The use of specific gravity measurements as an index of calcification is justified by the high degree of correlation between the two.^{6, 7} Also, comparison of carious teeth from this group with controls selected at random is allowable, for Black⁹ has shown that the specific gravity of

TABLE I. SPECIFIC GRAVITY OF DENTIN IN CARIOUS HUMAN TEETH EXTRACTED DURING THE LATTER MONTHS OF PREGNANCY

AGE OF PATIENT	MONTH OF PREGNANCY WHEN TOOTH EXTRACTED	CORONAL DENTIN		ROOT DENTIN	
		NO. OF SAMPLES	AVE. SPECIFIC GRAVITY	NO. OF SAMPLES	AVE. SPECIFIC GRAVITY
20	V	2	2.18	4	2.10
13	V	2	2.21	1	2.07
19	VI	-	--	5	2.17
19	VI	-	--	4	2.10
16	VI	4	2.17	4	2.13
35	VI	-	--	3	2.05
35	VI	1	2.16	3	2.16
35	VI	4	2.16	3	2.18
?	VI	2	2.13	5	2.10
22	VI	3	2.13	2	2.12
22	VI	1	2.10	2	2.10
19	VII	-	--	6	2.11
19	VII	4	2.16	6	2.11
19	VII	1	2.03	1	2.08
17	VII	1	2.16	3	2.13
?	VII	3	2.09	5	2.08
16	VIII	5	2.13	1	2.11
19	VIII	-	--	4	2.08
19	VIII	1	2.14	2	2.09
19	VIII	5	2.12	4	2.09
20	VIII	3	2.09	3	2.09
20	VIII	2	2.15	4	2.13
16	IX	-	--	4	2.12
16	IX	1	2.04	1	2.06
21	IX	3	2.12	2	2.14
15	IX	1	2.10	3	2.12
20	XI*	3	2.11	4	2.08
?	?	-	--	6	2.09
?	?	2	2.14	3	2.15
Averages			2.13		2.11
Averages of all samples (152), 2.12					

*Extracted 6 weeks post partum.

the sound portion of dentin varies neither with sex nor the presence of caries.

The specific gravity of dentin from the pregnant subjects is not significantly different from that of the nonpregnant group⁸ (Table II). Hence, it may be concluded that five to nine months of gestation withdrew no measurable amount of calcium salts from the dentin of these teeth. It is less probable that the relatively inert enamel was decalcified.

TABLE II. SPECIFIC GRAVITY OF DENTIN FROM PREGNANT AND NONPREGNANT WOMEN

	NO. OF TEETH	NO. OF DENTIN SAMPLES	AVE. SPECIFIC GRAVITY	RANGE OF SPECIFIC GRAVITY
Nonpregnant	14	40	2.08	1.82-2.22
Pregnant	29	152	2.12	2.03-2.21

No balance studies were made on these subjects, but the calcium intake, calculated from the institutional diets, was at most 1.6 Gm. per day. This amount of calcium may or may not have been adequate to maintain a positive calcium balance and also supply the fetal requirements.^{10, 11} Whatever the state of the calcium balance may have been, active caries was present without a measurable loss of calcium salts from the teeth. Apparently, therefore, neither gestation, per se, nor demineralization of the teeth was associated with caries in this group of women.

Summary

No significant difference could be found between the average specific gravity (index of the degree of calcification) of dentin from pregnant women and from other individuals. The average specific gravity for dentin of the pregnant group was 2.12 while that of the nonpregnant controls was 2.08.

It was concluded that gestation did not cause a withdrawal of calcium salts from the dentin and, therefore, the caries already present in this group of pregnant women was not associated with a metabolic demineralization of that tissue.

We are indebted to The Division of Dental Research, University of Rochester, Rochester, New York, for the use of its laboratories in carrying out part of the work. We also wish to thank Dr. Percy Howe of the Forsyth Clinic, Boston, and St. Vincent's Hospital, Philadelphia, for collecting the teeth.

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THE INFLUENCE OF THE PLACENTAL SITE UPON FETAL PRESENTATION

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THE placenta acts as a foreign body of similar dimensions within the cavity of the uterus and has a tendency to displace the fetus, requiring the latter to conform to the remaining intrauterine space. It has been shown^{1, 2} that the placenta usually occupies a discoid site comprising most of either the anterior or posterior wall. Snow and Powell,³ in 1934, were probably among the first to note the site of the placenta as viewed by roentgen ray. They studied their patients by both anteroposterior and lateral views. In most of their cases the placenta appeared on one anterior or posterior wall, and thus appeared only in the lateral view. They stated that "in practically all of 60 cases the ventral part of the fetus faces the placenta. In no instance was the fetal back flush up against it. This appears to be natural because the placenta is very compressible and the relatively smooth back of the baby might disturb the placental circulation. Very often, a knee or elbow causes a pressure defect in it. When a part does abut on it, a line of increased density appears between. For the elbow, it is usually about 2 mm., for knees about 3 mm., and for the buttocks as much as 1 cm. It is our belief that this is caused by the greater penetrability by roentgen rays of the fat-containing subcutaneous tissues. Incidentally this finding is often helpful in locating the placenta."

Five years later in a second paper, Snow and Rosensohn⁴ stated "in the diagnosis of the site of the placenta it was found that the structure could be seen in routine roentgen examinations of pregnancy in its late stages. The usual anteroposterior and lateral views were used but the lateral is more helpful. The placenta is seen as a soft tissue shadow which occupies about one-third of the wall space of the uterine cavity. It bulges in its middle where it measures about 7 cm. in diameter and tapers off at the periphery toward the uterine wall. The small parts of the fetus almost invariably face the placenta, and by pressure cause digitations in its substance. The subcutaneous tissues of the fetus, since they consist largely of fat, are highly penetrable by the roentgen rays and as a result, they leave a black line between the fetal parts and the placenta. For the elbow this may measure about 2 mm. and for the buttocks as much as 1 cm."

In the intervening years Dippel and Brown⁵⁻⁷ further developed the method of visualization of the placenta in the x-ray film, using mainly

the lateral soft tissue view. They found the placenta visualized in 90 per cent of 262 observations by lateral soft tissue roentgenography. No errors were found in 53 cases checked by reliable clinical methods. They found equal division of anterior and posterior wall implantations.

Inasmuch as our technique of taking the films, developed independently over the past several years, coincides almost identically with that described by Dippel and Brown,⁵ their paper is quoted: "The lateral film obtained by this method we believe to be the most important one in the study of the uterus and the product of gestation. Its correct interpretation requires not inconsiderable study and practice. If the film is properly taken, the posterior uterine wall may be clearly visualized with the aid of any viewing box, but the anterior abdominal and uterine walls which represent a much thinner area of tissue penetrated by the x-rays will be 'burned out,' i.e., over-exposed. However, by viewing those latter areas with a concentrated light, as with a 200-watt frosted bulb in an ordinary goose-neck lamp, with a shade, it can be as clearly made out as the posterior uterine wall and the latter's adjoining soft and osseous tissues."

Likewise their method of reading the films to bring out all of the meaning has been well stated by Dippel and Brown:⁶ "The technic of viewing soft-tissue plates is quite important. This is certainly true of lateral views, as we have thus far been unsuccessful in obtaining lateral roentgenograms of even density. The intensity of different areas varies so widely that strong illumination, as with a spotlight, can be used to marked advantage in the region of the anterior abdominal wall. Since the exposure is made to produce the maximum soft-tissue detail in the region of the posterior uterine wall, the anterior uterine wall, which represents much less thickness of tissue, is over-exposed."

Carty⁸ elaborated further: "The illumination with which soft tissue roentgenograms are viewed is of some importance. In all my cases, I like to use illumination of various colors, particularly green, red and blue, and often in this manner some soft tissue detail becomes apparent which otherwise might be lost. Also, I think it is of help to use a magnifying glass. Magnification methods depending upon projection of a certain portion of the film have not been successful, due probably to the relatively small difference in density of contiguous structures."

Material

In this study of 363 patients, practically all films were taken during the first stage of labor. We have found the value of the film to lie chiefly in its infallible ability to give the true presentation of the fetus, anteriorly and posteriorly. In addition, it gives the amount of engagement of the presenting part, the flexion of the head, the location of the placenta and some idea of the length of the true conjugate. The length of true conjugate and the diameter of the head are quite accurately obtained by applying to the midline of the abdominal wall a centimeter marked head rule which is usually done. A study is now in progress in regard to the measurement of the fetal head by this method compared to the actual measurement after delivery.

Furthermore, as brought out by Snow and his associates, and by Dippel and Brown, the lateral film is of marked aid in diagnosis in case of placenta previa and of premature separation of the normally implanted placenta.⁹ Most of the results of this study of the influence of the placenta upon the position and presentation of the fetus are shown graphically in the chart.

Previously in almost all of the papers, such as those of Melhado,¹⁰ Thoms,¹¹ Caldwell, Moloy, and D'Esopo,^{12, 13} Cosgrove,¹⁴ Calkins,¹⁵ and D'Esopo,¹⁶ on the subject of presentation, the main idea advanced was that the contour, shape, and size of the pelvis were the dominating features. Only now and then, as did Pennington, in a discussion of a paper on the subject,¹⁵ did anyone suggest that the placenta might have considerable influence. Likewise, Melhado¹⁰ stated that the placenta might be an etiologic factor, to wit: "May the true etiologic factor not lie in the uterus itself? With the placenta on the anterior wall, the child's back would more readily accommodate itself to the unoccupied posterior portion of the uterine cavity. This has frequently been proved by cesarean section."

TABLE I. SITE OF PLACENTA

PRESENTATION IN FIRST STAGE OF LABOR	ANTERIOR (163)		POSTERIOR (200)	
Occiput anterior	47	(29.5%)	117	(58.5%)
Occiput transverse	74	(44.7%)	60	(30.0%)
Occiput posterior	42	(25.8%)	23	(11.5%)

Fig. 1 reveals the following facts: there were a total of 363 cases, 176 white women and 187 colored women. (We excluded all breech cases, all indistinct films and those in which the placenta was not definitely outlined on either wall.) Among the white women, 80 placentas were located on the anterior and 96 on the posterior wall. In the colored women, 83 placentas were on the anterior and 104 on the posterior wall. Dippel and Brown noted equal distribution between the two walls. We, however, over a period of years, have made comment upon the fact that our series had more on the posterior wall, and we were of the opinion that 40 per cent were anterior and 60 per cent posterior. This study reduces the difference to 45 per cent and 55 per cent, but still it is seen to be appreciable and quite similar in the two races. For each year of study, the tallies were added in different colors and the ratios were found to be quite constant throughout.

From analysis of the figures noted in Fig. 1, it becomes apparent that in the 363 cases there were a total of 164 (45 per cent) occiput anterior presentations, 134 (37 per cent) occiput transverse presentations,* and 65 (18 per cent) occiput posterior presentations at the time of making the film in the first stage of labor. Still further analysis reveals that there were 163 cases with the placenta situated upon the anterior wall of the uterus. Among these, 47 (29.5 per cent) were associated with occiput anterior presentation of the fetus; 74 (44.7 per cent) with occiput transverse; and 42 (25.8 per cent) with occiput posterior presentation. On the other hand, 200 placentas were situated upon the posterior

*These are exact O.T. presentations. If they deviated more than five degrees, they became occiput anterior or occiput posterior.

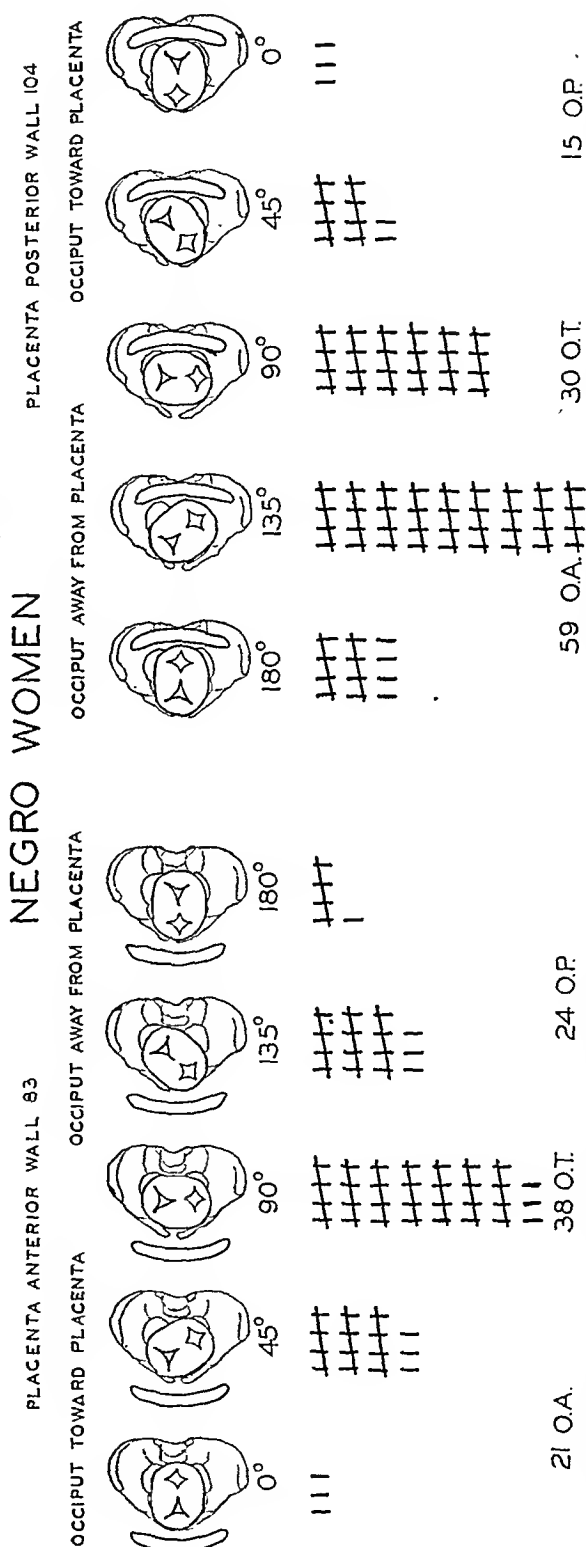
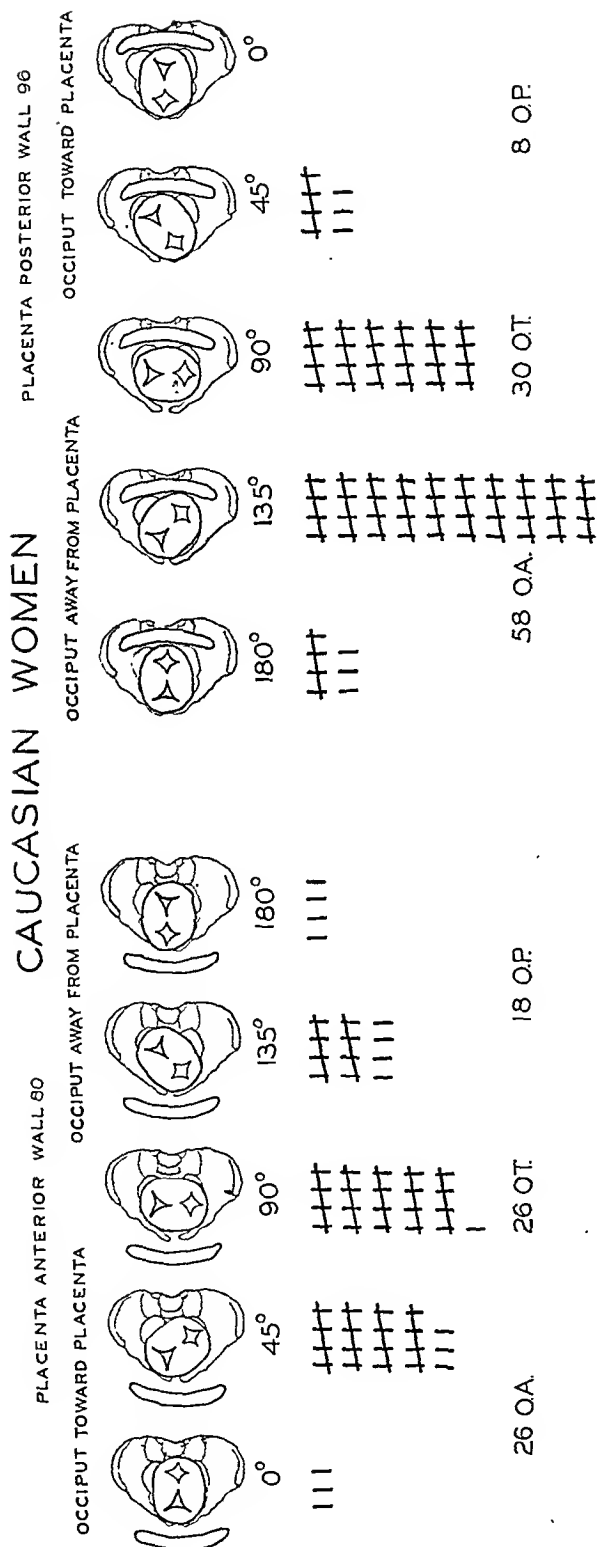


Fig. 1.—To the left of the midline the figures are represented with the placenta on the anterior uterine wall; to the right of the midline the placenta is represented as on the posterior uterine wall. The cephalic presentation is illustrated with the total number of such presentations tabulated below each figure. The placenta was on the anterior wall in 83 instances and on the posterior in 104.

wall in which the associated presentation of the fetus was 117 (58.5 per cent) occiput anterior, 60 (30 per cent) occiput transverse, and 23 (11.5 per cent) occiput posterior. Thus when the placenta was anterior, the incidence of occiput anterior presentations was only one-half what it was when the placenta was posterior, and when the placenta was anterior, the incidence of occiput posterior presentations was more than twice what it was when the placenta was posterior. Furthermore, occiput transverse presentation was 50 per cent more common when the placenta was anterior than when it was posterior.

Elsewhere,² it has been shown that the pregnant uterus is like an irregularly globular bag, wider at the fundus than its anterior posterior diameter. Now the cavity of this bag has been shown to have two essentially foreign bodies pressing into it either from one anterior or posterior wall, or into both; one of these is the bulky placenta and the other is the promontory of the maternal spine. Calkins¹⁵ intimates that the full urinary bladder may also be a factor. The fetus, on the other hand, is essentially a parallelepiped with one concave ventral surface opposing a convex dorsal surface. Now when this geometric figure lies in the uterus, the great tendency is for the convex dorsum to lie opposite, or at least not toward the greatest indentation which is no doubt the promontory, after any degree of depression into the true pelvis has begun. However, the placental foreign body probably has a tendency to alter this position accentuating its effect, if it happens to lie on the same wall (the posterior) as the promontory, and a tendency to cancel the effect if it lies on the anterior wall. Of course, the shape of the pelvic inlet must have some effect upon presentation, a wide gynecoid inlet probably having a tendency to occiput transverse presentation, while a narrow anthropoid inlet quite certainly stimulates occiput anterior or occiput posterior presentation. In fact, that may well account for the main difference in this chart study between the white and colored patients. Occiput posterior presentation incidence is almost twice as high in Negro as in the white patients. It has been shown previously¹⁷ that the Negro women have twice as great an incidence of anthropoid pelvis as the Caucasians.

Conclusions

1. The great majority of placentas in human beings are located upon the anterior or the posterior wall of the uterus.
2. The ratio found in this study was 45 anterior to 55 posterior. These figures are exclusive of placentas of other sites which are relatively infrequent. This ratio was the same in both races studied.
3. The placenta located on the anterior uterine wall had a definite tendency to production of occiput posterior presenting fetuses. Mathematically when the placenta was anterior, the chance for occiput posterior presentation of the fetus was double what it was if the placenta was posterior (25.8 per cent to 11.5 per cent).
4. The placenta located on the posterior uterine wall had an increased tendency to produce occiput anterior presentations in the fetuses. In this case, when the placenta was on the posterior wall, the chance of the presentation being occiput anterior was twice what it was if the placenta was anterior (58.5 per cent to 29.5 per cent).

5. The incidence of occiput transverse presentation of the fetus in the first stage of labor was 30 per cent if the placenta was located on the posterior wall and 44.7 per cent if located on the anterior wall.

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Ayre, J. E.: The Role of the Corpus Luteum in the Toxemia of Pregnancy, Canad. M. A. J. 44: 575, 1941.

A possible explanation of the etiology of toxemia of pregnancy due to a disturbed endocrine balance, with the master gland of pregnancy, the corpus luteum, and the trophoblast of the placenta playing the major roles. Hypersecretion of these elements in toxemia produce an uncompensated endocrine imbalance and this has been advanced as the basic cause of excessive relaxation of all smooth muscle of the body (uterus, vascular system, bowel, ureters, etc.) which in turn lead to edema and other changes in organs of great vascularity, such as the liver, kidneys, uterus, and brain.

The use of vitamin B₁ as an antagonist to progesterone is suggested.

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CAUDAL ANESTHESIA FOR CESAREAN SECTION

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THE reintroduction of caudal block into our obstetric armamentarium once again demonstrates the cyclic trend so frequently seen in the course of medical progress. Medications, techniques, and the like, once popular, suddenly find themselves discarded only to be resurrected and accepted with renewed enthusiasm at some later date. So, too, with caudal block. Although extradural anesthesia, introduced via the sacral hiatus, has been utilized in obstetrics intermittently since the early part of this century, certain innovations have contributed to its recent popularity. To the availability of an anesthetic reagent of low toxicity yet of suitable efficacy can be attributed, in some part, the relative safety of the procedure. A technique devised for its continuous administration, as promulgated by Hingson and Edwards, throughout the course of the entire first, as well as the second, stages of labor has been made available. Furthermore, the service of caudal block has been extended to abdominal cesarean sections by taking advantage of the fact that the height to which the anesthetic solution dissects its way under pressure extradurally is directly proportional to the volume injected.

The scope of this paper embraces forty-eight cesarean sections performed under the single injection technique of caudal anesthesia. For the most part, forty-three cases, the series was derived from private practice; only five cases were obtained from the charity service of the Milwaukee County Hospital.

TABLE I. INDICATIONS FOR THE OPERATIONS

Previous cesarean	16
Cephalopelvic disproportion	12
Premature separation of the placenta	5
Toxemia without convulsions	4
Malpresentation	3
Placenta previa	2
Dystocia	2
Toxemia with convulsions	1
Previous extensive vaginal plastic	1
Previous stillbirth in an elderly primipara	1
Fetal distress	1

None of the sixteen women with whom previous section is listed as indication was permitted to fall into active labor. Although it is not our practice to routinely subject a woman to section because of a previous cesarean, it might be mentioned that none of this group had

ever in the past been delivered of a live baby *per vaginam*. On the other hand, all twelve of those listed under cephalopelvic disproportion were given the benefit of an adequate test of labor. The two listed under the ambiguous term, "dystocia," include instances where the cervix failed to efface and dilate and an attempt at delivery through the normal channels, even with the benefit of Dührssen's incisions, was not deemed advisable. Three stillborn infants were obtained where abruptio placenta occurred. In none of the five instances where premature separation of the placenta existed was extirpation of the uterus necessitated. The four toxemia-without-convulsion patients included one case of chronic glomerulonephritis and three of fulminating pre-eclampsia where conservative measures were not availing. The single case of eclampsia was well controlled at the time of operation. The three instances of malpresentation include one transverse presentation and two cases, which we cite with due apologies under the heading of malpresentation, of large frank breech presentations where, after an ample trial of labor, section was resorted to in the interest of the infant. The woman in whom a previous vaginal plastic was considered as indication had undergone an anterior and posterior colpoperineorrhaphy and trachelorrhaphy. Both instances of placenta previa were of the complete type. In the one instance where fetal distress of undetermined etiology occurred, cesarean section was resorted to as the most rapid as well as the safest method, under the existing circumstances, of expediting delivery.

This series is comprised of forty-six laparotrachelotomies and two Porro cesareans. In no instance was a classical section performed. Three of the women were subjected to a Madlener sterilization.

The only postoperative complication worthy of note was a pelvic abscess which developed in a primipara subjected to a low cervical section after a protracted labor.

The anesthetic agent used for the series was a 2 per cent solution of metyeaine (Gamma/2 methyl-piperidino/-propyl benzoate hydrochloride). There was some variation in the volumes injected. In two of the patients, 40 c.c. were injected; in four cases, 45 c.c. were used; in two instances, 50 c.c. were administered; and in the remaining forty, 60 c.c. of the metyeaine were given.

All of the patients received a barbiturate preoperatively. Four of the series were given 3 grains of sodium amytal, while seven received 3 grains of pentobarbital; and the remaining received $4\frac{1}{2}$ grains or more of pentobarbital. All but nine were given a preoperative hypodermic injection of atropine sulfate gr. $\frac{1}{150}$.

The lateral decubitus position of the patient at the time of injection was used with thirty-nine of the subjects; the knee-chest position with nine.

In three of the forty-eight cases, the block failed completely. That the cause for the failures is due to faulty technique on the part of the

operator is acknowledged. It must be assumed that a potent anesthetic agent, once instilled into the sacral canal, will anesthetize the nerves it bathes and that in those instances where anesthesia and analgesia fail to occur, the solution had, in all probability, never been properly introduced into the sacral canal. The complete failures were supplemented by inhalation anesthesia. In two instances the caudal block wore off before the operation was completed. Here, closure of the abdomen was affected under intravenous sodium pentothal. In one instance analgesia resulted but the anesthesia on the anteroabdominal wall failed to rise sufficiently high to permit an adequate incision. This patient's block was complemented by nitrous-ether anesthesia.

There were no maternal deaths in the series; none of the three fetal deaths could be attributed to the anesthetic or the type of its administration.

The development of satisfactory anesthesia is comparatively slow. The operator must expect to allot a latent period up to twenty minutes to transpire between the time of injection of the anesthetic to the time when an abdominal incision can be made without discomfort to the patient.

Untoward effects were occasionally witnessed. A sudden transitory fall in blood pressure was seen not infrequently, particularly in those instances where larger volumes of the anesthetic agent were instilled. In over half of the subjects a temporary slowing of the fetal pulse was noted for several minutes following the injection. In this series of forty-eight cases, the absence of such transient untoward reactions as jaetitation, disorientation, hallucinations, etc., which we have witnessed at other times with caudal block, might be attributed to the preoperative administration of barbiturates. Whether purely coincidental or whether the barbiturates antidote toxic effects of meteyaine is a matter of conjecture.

Invaluable for operative obstetrics, and particularly suited for cesarean sections, caudal block, not at all unlike spinal and inhalation anesthesia, defies promiscuous use and demands a certain degree of consideration and respect. That the procedure must be attended to with strict caution and assiduous regard cannot be overemphasized. An inadvertant intravenous or intrathecal, rather than extradural, injection will result in alarming reactions and may even terminate in a disastrous fatality. It is essential that scrupulous asepsis be observed in the technique lest pathogenic organisms be introduced into the areolar bed within the sacral canal, a fertile culture medium. Furthermore, not all women are suitable candidates for the procedure. Subjectively, the neurotic or apprehensive patient may vehemently object to even the suggestion of being permitted to remain conscious throughout her delivery. Objectively, in the obese woman with thick subcutaneous areolar sacral pads, identification of the bony landmarks may be so obscured as to make injection well nigh impossible.

In the appraisal of caudal anesthesia, what are the advantages of its use for cesarean sections? The paramount consideration of the obstetrician in attendance is, of course, the safety of the parturient and the welfare of her newborn. It befalls his oft-unhappy lot to decide not only on the indication for this type of surgical procedure—an operation of major importance with two lives involved—but he must recognize that the choice of anesthetic he will use will be as important as the surgical technique he will follow. He must appreciate that his patients are frequently seriously imperiled even before the cesarean is begun. The mother may be exhausted by the efforts of a prolonged labor; she may be shocked by the abrupt separation of her placenta; she may be exsanguinated by the hemorrhage of a previa; she may be ill with cardiovascular, renal or pulmonary disease. Similarly, the infant she bears may already have been subjected to the insult of a difficult labor, of embarrassed circulation, of toxemia, or of medullary depressants. Other matters to be considered are, that the infant is premature, perhaps barely viable; the mother is unprepared for an inhalation anesthetic; patients may vomit, with subsequent aspiration, atelectasis, pneumonia; ileus and other postoperative complications, any or all the price of a suprapubic delivery.

Caudal anesthesia then, is well suited for cesarean sections. A single injection of 60 c.c. of the anesthetic agent introduced into the sacral canal offers the laboring parturient relief from pain, relief from the attendant excitability, and produces abdominal anesthesia of ideal duration, of minimum length, yet consistent with efficiency and safety. The patient may be placed in the Trendelenburg position so that gravity displaces the unnecessary handling and packing of abdominal contents away from the operative field. Inasmuch as the uterus retains its tone, blood loss is minimal. The placenta separates without delay. The complete relaxation facilitates closure of the abdomen. The incidence of post-partum hemorrhage is diminished. The patient is comfortable on her return to bed and may be given fluids and food immediately after operation. Her puerperal convalescence is undisturbed and the subsequent involution of the pelvic organs is not influenced. The advantages over inhalation anesthesia are evident: there is no first-stage excitement, no vomiting, no danger of explosion; there is no irritating effect on the respiratory passages; no alteration in acid-base metabolism; nor any of the shock and dehydration which accompany prolonged inhalation anesthesia. The method can be used with comparative safety in patients with cardiovascular, pulmonary, or renal complications. Insofar as the infant is concerned, there is no immediate or remote hazard to its welfare which could be attributed to the anesthetic. In the elective cases, depression of the medullary centers is absent; the newborn's cry is spontaneous and lusty; in the emergency cases, asphyxia requiring resuscitation can, in all fairness, be attributed to the complications which demanded the cesarean rather than to the choice of anesthetic used.

Summary

The use of the single-injection technique of caudal block in a series of forty-eight cesarean sections is reviewed. That the method is not devoid of dangers is stressed. The precautions which must be exercised in its use are emphasized. The advantages and disadvantages of this type of anesthesia are discussed.

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AN ANALYSIS OF 250 CASES OF POSTMATURITY

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THE subject of postmaturity is one about which very little has been written. The few papers about it have defined postmaturity, for the most part, in terms of the size of the infant. The problem of postmaturity in relation to the expected date of confinement is also important. The question continually arises as to whether or not the patient who is overdue should have labor induced. On the one hand, the obstetrician is faced with (1) a fretful patient who demands that she be delivered, (2) the fear of the ever increasing size of the baby, and (3) the fear, which is prevalent, that the baby may die in utero. On the other hand there is the feeling that the patient is doing very well and that it is meddling to interfere. It was in an attempt to find out just what happens to the postmature patient and her baby that this study was undertaken.

It is admittedly difficult to determine which patient is postmature. For this study a patient was considered postmature who was 295 days or more beyond the first day of her last menstrual period, or in other words, 15 days or more beyond her expected date of confinement. Any patient was excluded who was not sure of her last period or whose uterus at the time of her first clinic visit (usually at 4 to 6 months) was not consistent in size with her menstrual dates. In this manner it was hoped to eliminate as many who were not truly postmature as possible.

Material

A total of 3679 consecutive records was reviewed. Of these, there were 3289 deliveries of viable (28 weeks or over) babies. Postmaturity, as defined above, occurred 250 times. Thus, there was an incidence of 7.6 per cent, or 1 in every 13.2 deliveries. This figure agrees closely with the incidence of 7.3 per cent in 9649 cases reviewed by Clayton,¹ who used 294 days as his defining point. We see therefore that the problem arises rather frequently.

Of the postmature cases, 66 per cent were primiparas and 34 per cent multiparas. This is exactly the ratio of primiparas to multiparas in the total records studied.

There were four patients who exceeded their expected dates of confinement by 39, 42, 44 and 48 days respectively. The distribution of the other 246 cases appears in Figure 1, following a curve as might be expected. This curve may be superimposed almost exactly on the comparable portion of the curve of Hotelling² for the number of deliveries per day of pregnancy plotted for several thousand deliveries. The average time of delivery for the primiparas of my series was 19.4 days beyond the expected date of confinement, while the multiparas averaged 20.2 days overdue.

The belief that postmature babies are heavier than term infants was found to be true in this series. The average weight of 600 term babies delivered during the period from which the postmature records were taken was 7 pounds, 3 ounces for the infants of primiparas, and 7 pounds, 10 ounces for the infants of multiparas. The average weight of the postmature babies of primiparas was 7 pounds, 12 ounces, a gain of 9 ounces. The postmature infants of multiparas averaged 10 ounces more than the term babies, or 8 pounds, 4 ounces. Since this involves a series of fairly large numbers, there can be little doubt as to the validity of the figures.

In an attempt to break down further the figures on the weights of the babies, the weights of the postmature infants were averaged in two groups. One group consisted of those delivering between 15 and 19 days postmaturely, and the other group of those delivering 20 days or more after their expected date of confinement. Surprisingly, the infants of primiparas in the first group averaged 7 pounds, 13½ ounces, while those who were 20 or more days postmature averaged only 7 pounds, 9½ ounces. The infants of multiparas showed the earlier group to be about 1 ounce heavier, averaging 8 pounds, 4½ ounces, in contrast to 8 pounds, 3½ ounces for the more postmature group.

This apparent loss of weight in the later days of postmaturity is difficult to explain. It may be that splitting the series up into smaller groups has invalidated the figures. It may also mean that after a certain time the aging placenta ceases to nourish the fetus as well as formerly, stopping development and causing the fetus to begin to live off of its stored resources. However, the marked gain in weight shown by the group as a whole seems to indicate clearly that the postmature mother is faced with the problem of delivering a larger fetus than she would have delivered at term.

The fact that the babies are larger leads one to surmise that labor would be longer in the postmature group. The average length of labor for 500 mothers at term who delivered in the same months and with the same analgesia as the postmature mothers was 14.9 hours for primiparas and 8.8 hours for multiparas. The postmature primiparas were in labor an average of 18.2 hours, while the multiparas were in labor 10.5 hours. Thus, the postmature primiparas were 3.3 hours longer in labor, while the multiparas required 1.7 hours longer.

One might also surmise that operative intervention would rise with the increase of weight of the fetus and the length of labor. This was the case. The number of operative deliveries, excluding breeches (of which there were 6), rose from a clinic percentage for the period of 24.4 per cent to 30.8 per cent, or an increase of 6.4 per cent.

When the operative figures are broken down, we find a marked increase in the more serious types of operations. There were 5 midforceps in the 250 postmature cases. This is far above the usual clinic ratio, as midforceps are rarely done. There were three Waters' extra-peritoneal cesarean sections done. This again is a much higher ratio than the clinic ordinarily runs. The numbers of low forceps and transperitoneal cesareans were not increased remarkably.

The morbidity might be expected to rise because of the aforementioned conditions. The increase was marked. The postmature patients had a morbidity of 12.4 per cent, against a clinic morbidity for the same period of 4.7 per cent. Retention of lochia, cystitis and intra-uterine infection, in that order, accounted for most of the morbidity.

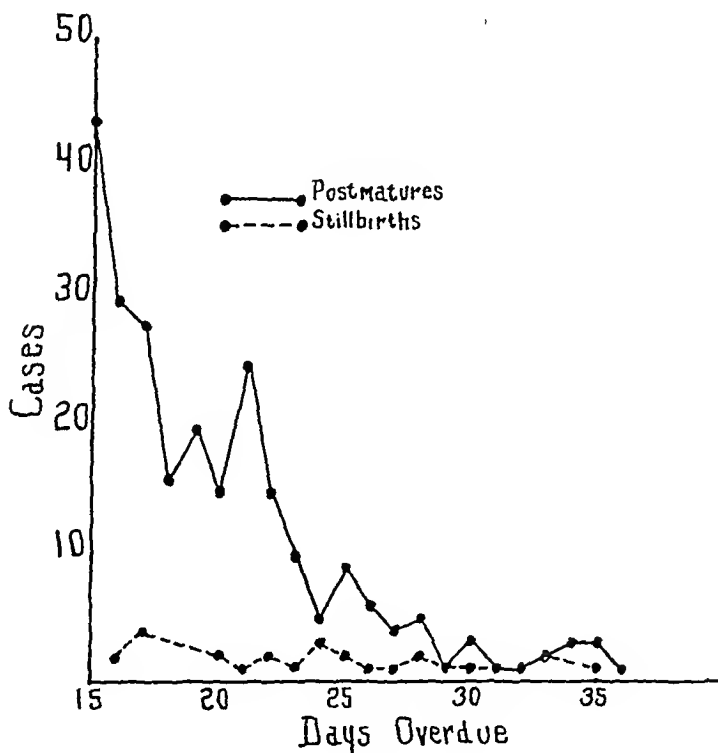


Fig. 1.—Showing distribution of postmature infants and stillbirths.

There is a definite belief among obstetricians that postmature infants tend to die in utero. Consequently, considerable time was spent in studying the stillbirths in this series and a series of consecutive clinic stillbirths. There were 13 stillbirths in 250 postmature births, or 5.2 per cent. Clayton¹ found a stillbirth rate of 6.5 per cent in his postmature series. The clinic stillbirth rate for viable (28 weeks or over) infants over the 1½ years covered by this paper was 2.5 per cent. However, 43 per cent of these were due to prematurity. For comparison with the postmature group, it seems fair to disregard the prematures, as obviously none of the postmature died of prematurity. So we find a term stillbirth rate in the clinic of 1.4 per cent, compared to a rate of 5.2 per cent for the postmatures.

The distribution of postmature stillbirths does not follow the curve of distribution of cases in Fig. 1. Stillbirths were scattered evenly throughout the postmature period. The average number of days post-

mature was 24.4 per cent, or somewhat longer than the average for living infants.

In an attempt to ascertain the cause of the increased stillbirths, a separate series of 186 consecutive stillbirths, including the 13 post-matures already mentioned, was studied. Of these 27, or 1 case in 6.9, were postmature, substantiating the feeling that stillbirths were increased in postmaturity, since 1 in 13.2 normal cases was postmature. Prematurity accounted for 84 cases of stillbirths.

The term and postmature stillbirths were separated, and each group was then divided into a subgroup of those dying before or during labor. Each subgroup was then divided into those for which a cause of death could be determined and those for which no cause could be ascertained. Cause of death during labor embraced many things such as prolapsed cord, difficult forceps or breech delivery, destructive operations for hydrocephalus, etc. Causes of death before labor were erythroblastosis, pneumonia in the mother, and the cord wound tightly about the neck. Of course, it can not be proved that the last was the cause of death, but it was noted as such in the record. Table I shows the number and percentage of cases in each group.

TABLE I

DEATHS	MATURE		POSTMATURE	
	NUMBER	PER CENT	NUMBER	PER CENT
Before labor				
No cause	12	16.0	5	18.5
Cause apparent	7	9.3	5	18.5
During labor				
No cause	7	9.3	3	11.1
Cause apparent	49	65.6	14	51.9

The series is too small to expect perfect agreement of the percentages in Table I. It would seem to be clear from these figures that there is no great difference between the cause of death in the mature and post-mature stillbirths. Certainly there would seem to be no increase in the number of babies who died for no apparent cause, which is what popular opinion would lead us to believe. Clayton¹ also concluded that there was no increase in stillbirths without evident cause in post-maturity. The only difference which might be important is the difference of those dying before labor where the cause was 'apparent. This was caused by the appearance of the same number of erythroblastotic stillborns (3) in each series despite the larger series of term infants.

It should be noted that there were no stillbirths in the postmature group from premature separation of the placenta. One might think that premature separation of the placenta might be a frequent cause if degeneration of the placenta took place. The age of the mothers of stillborn infants did not vary from the average age of the series mothers.

Although the series is small and consequently the figures open to question, it would seem that postmature infants are no more inclined to die for no apparent reason than term infants. It can not be denied that there seems to be a tendency for the postmature infant to succumb more easily than the mature to the various trials that beset him, or because he is bigger and, better developed the trials are more strenuous.

It is interesting to note that study of a large number of postmature placentas led Reynolds² and Masters and Clayton⁴ to conclude that

postmature placentas showed no increase in degeneration over mature placentas. This gives added weight to the thesis that infants do not die of postmaturity alone.

There were 2 neonatal deaths in the 250 cases. One was caused by diaphragmatic hernia and one by erythroblastosis. A study of the living infants' post-partum-weight charts showed no striking difference from those of the term infants.

There was one maternal death. The patient died of hemorrhage and shock following a long labor terminated by Waters' extraperitoneal cesarean section. So we see that increased difficulty in labor is not without danger to the mother as well as to the child.

Conclusions

A series of 250 carefully selected, consecutive cases of mothers who delivered at least 15 days beyond their calculated date of confinement was studied, together with an additional series of 186 consecutive stillbirths. Postmaturity occurred once in 13.2 deliveries. Postmature infants were significantly heavier than term babies at birth. However, they seem to lose the tendency to gain after they are 20 days postmature. Coincident with the increase in weight is an increase in the length of labor; an increase in the operative rate, especially in the more serious operations; and a marked increase in morbidity.

The stillbirth rate was definitely increased. This was an increase in the deaths with apparent cause rather than in deaths where there was no cause except postmaturity. The stillbirths were longer postmature on the average than the general series, averaging 24.4 days beyond term as against 19.6 days for the 250 patients.

The babies who were born alive showed no increase in neonatal deaths nor any difficulty in the post-partum period.

The question as to what to do about postmaturity has not been answered. The increase of difficulty found in postmature patients is not of sufficient magnitude to warrant drastic measures to keep patients from becoming postmature.

The answer to the problem probably lies in the realization that it exists. Each case should be watched individually. If the cervix is favorable, induction of labor is indicated. If it is not, then the size of the fetus must be carefully evaluated against the size of the mother's pelvis, and a close watch must be kept on the increasing size of the fetus. No more fear need be entertained that the fetus will be lost in utero without cause than exists at term. However, failure to appreciate the fact that labor may be more difficult and to prepare to meet these difficulties may cost the baby its life or even the mother hers.

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CLINICAL EXPERIENCES WITH PYRIDOXINE HYDROCHLORIDE IN TREATMENT OF NAUSEA AND VOMITING OF PREGNANCY

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VOMITING is always an annoying and not infrequently a serious complication of pregnancy. Numerous methods have been advocated for its relief without any uniform degree of success. For some time we have used mild sedation (phenobarbital), restriction of fluid intake and Vitamin B₁ in the milder cases, and sedation, bed rest, plus intravenous glucose in the more severe cases, with considerable success; however there were still many instances where this regime was only partially successful or failed. Recently our attention was directed to an article of Willis and his co-workers, who reported the successful use of Vitamin B₆ in hyperemesis gravidarum. A supply of pyridoxine hydrochloride* being made available, we first used this therapy upon a patient who had been treated with other methods without success. The results were so good that we introduced the use of the drug as a method of routine and have now used it in 32 patients. We will continue to use it on a more extended series of cases.

In studying these patients an attempt was made to grade the severity of nausea and vomiting in order to express with some degree of uniformity the degree of nausea and vomiting present: Morning nausea was considered (1+) Group 1; nausea extending throughout the day (2+) Group 2; nausea and occasional vomiting (3+) Group 3; nausea and vomiting of a degree prohibiting the retention of any fluids or solids (4+) Group 4. While most of our patients fall into Group 1, the response of patients to therapy was seemingly not dependent upon the severity of nausea and vomiting present since several patients of Group 4 responded as readily as those of Group 1.

In all cases an initial dose of 50 or 100 mg. was administered intramuscularly, followed by injections of 50 to 100 mg. three times weekly until nausea subsided. Some patients reported favorable response with the first injection. In the most severe cases relief was not attained until the third or fourth injection. The largest amount given to any one patient was 1,050 mg.

Discussion

We were gratified by the rapid response to therapy. There were no untoward reactions to the drug. While the dosage we used was considerably larger in general than that employed by Willis and his associates, it is probable that smaller dosage would give equally good results.

All of these patients were treated with intramuscular injections. Since this series was started pyridoxine hydrochloride has been made available in tablet form, and we are currently observing a group of pa-

*Pyridoxine hydrochloride was supplied through the courtesy of the Winthrop Chemical Company.

tients who are being treated by oral administration of pyridoxine hydrochloride.

The results obtained in the patients of Group 1 are not remarkable since most of the patients probably would have responded to other types of therapy; however the rapidity of relief is noteworthy. The response in the more severe types, and especially in the Group 4 is more striking. This type of patient who has not infrequently required hospitalization may be effectively and economically treated with pyridoxine hydrochloride at home.

While the administration of pyridoxine hydrochloride appears to be of great value we feel that the importance of sedation and proper instruction as to diet should not be overlooked, but should be prescribed as usual, with pyridoxine hydrochloride as a valuable adjunct in the therapy of nausea and vomiting of pregnancy.

Conclusions

1. Complete or considerable relief from nausea and vomiting of pregnancy was obtained in a group of 32 patients who were treated with pyridoxine hydrochloride in dosages of 50 to 100 mg. three times weekly, receiving total dosages varying from 150 to 1,050 mg. injected intramuscularly.

TABLE I. GROUP I. (GRADED AS 1+, MORNING NAUSEA ONLY)

PATIENT	DOSAGE	TOTAL DOSAGE MG.	RESULTS
L. K.	50 mg. I,* 50 mg. 3 t.i.w.	150	Good
C. S.	50 mg. I, 50 mg. 3 t.i.w.	250	Good
P. L.	50 mg. I, 50 mg. 3 t.i.w.	150	Good
R. T.	50 mg. I, 50 mg. 3 t.i.w.	300	Good
M. E.	50 mg. I, 50 mg. 3 t.i.w.	400	Good
M. K.	100 mg. I, 50 mg. t.i.w.	300	Good
E. V.	50 mg. I, 50 mg. t.i.w.	500	Nausea still occurs, though less often
M. N.	50 mg. I, 50 mg. t.i.w.	450	Good
H. P.		150	Good
J. G.		200	Good
A. R.		350	Good
P. W.	100 mg. I, 50 mg. t.i.w.	450	Poor, nausea occasionally, but not as severe. (Patient was incidentally markedly anemic)
E. Y.	50 mg. I, 50 mg. t.i.w.	200	Good
F. C.	50 mg. I, 50 mg. t.i.w.	200	Good
R. E.	50 mg. I, 50 mg. t.i.w.	250	Good
L. C.	50 mg. I, 50 mg. t.i.w.	300	Good

*I = Initial dose.

TABLE II. GROUP II. (GRADED AS 2+, NAUSEA EXTENDING THROUGHOUT DAY)

PATIENT	DOSE	TOTAL DOSAGE MG.	RESULT
E. S.	50 mg. I,* 50 mg. t.i.w.	400	Good
R. P.	100 mg. I, 50 mg. t.i.w.	450	Good
H. T.	100 mg. I, 50 mg. t.i.w.	350	Good
L. P.	50 mg. I, 50 mg. t.i.w.	400	Good
A. D.	50 mg. I, 50 mg. t.i.w.	600	Good
P. J.	50 mg. I, 50 mg. t.i.w.	650	Good

*I = Initial dose.

2. Of the 16 patients with nausea confined to the morning 14 were completely relieved; 2 were partially relieved (Table I). Of the 6 patients with nausea extending throughout the day all were completely relieved (Table II). Of the 4 patients having nausea and occasional vomiting 3 were completely relieved; the fourth showed but slight improvement (Table III).

TABLE III. GROUP III. (GRADED AS 3+, NAUSEA AND OCCASIONAL VOMITING)

PATIENT	DOSE	TOTAL DOSAGE MG.	RESULT
L. D.	100 mg. I,* 50 mg. t.i.w.	700	Good
F. S.	100 mg. I, 50 mg. t.i.w.	750	Good
R. L.	100 mg. I, 50 mg. t.i.w.	600	Good
M. Q.	100 mg. I, 50 mg. t.i.w.	900	Poor, nausea persisted; patient vomited less after 250 mg. but never received complete relief.

*I = Initial dose.

All of the six patients with nausea and vomiting so severe as to make impossible the retention of food were relieved. This group showed the most striking and gratifying response (Table IV).

TABLE IV. (GRADED AS 4+, NAUSEA AND VOMITING SUFFICIENTLY SEVERE TO PREVENT RETENTION OF ANY FOOD)

PATIENT	DOSE	TOTAL DOSAGE MG.	RESULT
M. J.	100 mg. I,* 100 mg. t.i.w.	600	Good
D. G.	100 mg. I, 100 mg. t.i.w. x3, 50 mg. t.i.w.	750	Good
M. P.	100 mg. I, 50 mg. t.i.w.	1050	Good
H. B.	100 mg. I, x4, 50 mg. t.i.w.	850	Good
R. C.	100 mg. I, 50 mg. t.i.w.	600	Good
D. E.	100 mg. I, x3, 100 mg. t.i.w.	900	Good

*I = Initial dose.

3. No untoward effects were noted.

4. While the use of pyridoxine hydrochloride has proved of value in these 32 patients, the importance of sedation and adequate dietary supervision should not be overlooked, but should be prescribed as usual with pyridoxine hydrochloride used as an integral and valuable portion of this regimen.

5. Our series is being extended and observations are also being made with the use of orally administered pyridoxine hydrochloride.

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CARCINOMA OF THE VULVA AND VAGINA IN INFANCY

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CARCINOMA of either the vulva or vagina is very rare in infancy. Ritvo, Houghton, and McDonald,¹ Scotti,² Kellert,³ and Dargeon,⁴ writing on the subject of malignant tumors in childhood, report no cases of carcinoma of the vagina or vulva. Ewing⁵ points out that the tumors occurring during the first decade of life are those likely to be characteristic of the juvenile types of tumors. Malignant epithelial tumors represent a small minority of those occurring during this period of life.

Morse,⁶ upon reviewing the literature, states that carcinoma of any part of the female genital tract is rare in childhood. In his review he found only two instances of malignant epithelial growths of the external female genitals in children. The growth in one case originated in the vulva. The other case was that of an eight-month-old child in whom an adenocarcinoma extended from the wall of the vagina to the anterior cervical lip.

Kelly,⁷ in a paper on cancer in children, reports that gynecologic cancer is seldom encountered in children. He reports no case of carcinoma of the vulva or vagina in infants, except to refer to the vulvar case previously referred to by Morse and noted above.

In 1931 Baldwin⁸ reviewed 905 cases of carcinoma of the uterus, vagina, and vulva occurring at the University of Michigan. The youngest patient in his series was a girl of fourteen years who had a primary carcinoma of the vagina. He searched the literature for cases occurring in patients twenty years old or younger. Concerning the vagina he found only one case in a child. This case was reported by Heckford⁹ in 1868. The growth was said to be a villous medullary carcinoma protruding from and distending the vagina of a child ten months old. Heckford's article has not been available to us. Baldwin found no definite case of carcinoma of the vulva in an infant. Reference was made to a vulvar tumor occurring in a child of eighteen months, reported by Bietrix and by Thomas,¹⁰ but the latter originally described the growth as a sarcoma.

Lövegren¹¹ reports the case of a malignant papillary epithelial tumor of the vagina occurring in a child of seventeen months of age. Symptoms had been present only three weeks. Three months later the growth had extended to the vulva, and the patient died six months after the onset of the disease.

The rarity of malignant epithelial tumors of the vagina and vulva in infancy might lend interest to the following case:

Case Report

D. J. was a full-term child, the product of a normal spontaneous delivery on June 6, 1934. Her maternal grandmother died with cancer of the stomach. Her father and mother and six siblings were alive. The father was said to have pulmonary tuberculosis.

She had had no illnesses until she was five months old. At that age she developed a purulent blood-streaked vaginal discharge. For the following ten months there was little change in the character of the discharge. None of the various treatments which she received was effective. She became sallow and lost weight. In October, 1935, when

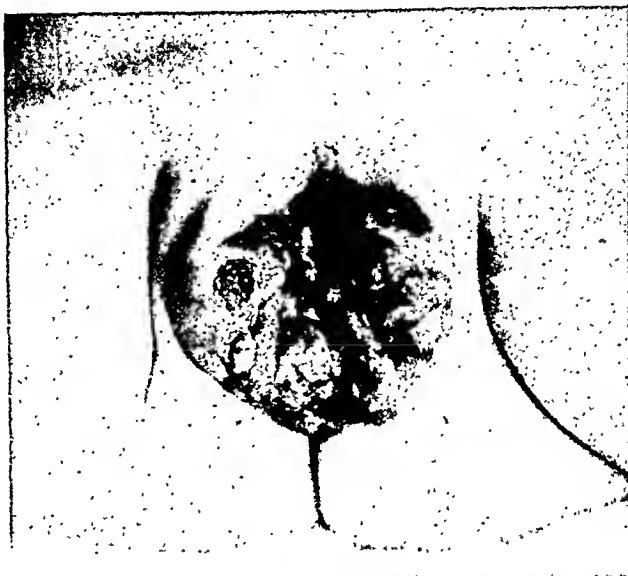


Fig. 1.—Adenocarcinoma of vulva before treatment. Patient was 21 months old.



Fig. 2.—Photomicrograph of frozen section of lesion seen in Fig 1. Diagnosed adenocarcinoma, Grade IV.

she was sixteen months old, a swelling appeared on the right labium which ruptured and discharged blood and pus. One month later a similar swelling appeared on the left side. This likewise ruptured and drained pus. During the succeeding months the lesion enlarged. It was described as "proud flesh" and was not remarkably painful.

She was first seen by us on admission to the Hospital in March, 1936, when she was twenty-one months old. At that time there was a very friable, easily bleeding, cauliflower mass, somewhat spherical in shape with a diameter of 5 cm. The center of the growth was at the lower portion of the introitus near the posterior commissure. The growth extended into the labia on each side, further on the left. The sites of the ducts of Bartholin's glands were included in the mass. The mass extended into the vagina for a distance of about 2.5 cm. above the introitus, involving the posterior and lateral walls of the vagina. The anterior wall was free. The cervix was not involved. Some areas of the tumor were so soft that semisolid tissue exuded on pressure. Smaller areas were harder. In the left side of the pelvis, and palpable through the vagina, there was a firm, bean-shaped, movable mass about 1 cm. in length, believed to be an enlarged iliac lymph gland. Smaller shotty glands were palpable in each inguinal region. Tissue was re-

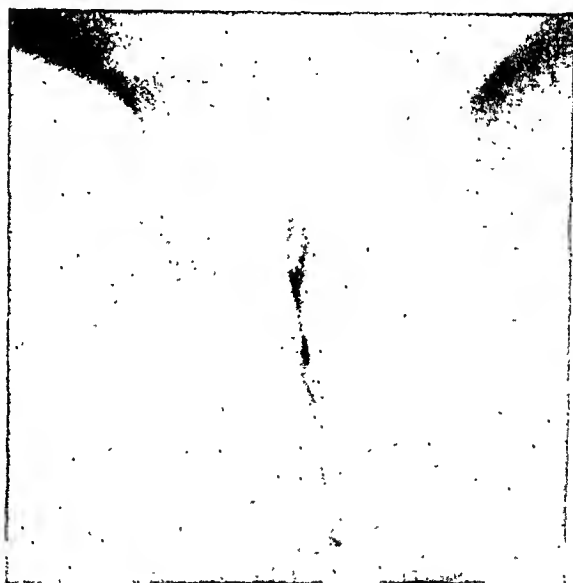


Fig. 3.—Same patient as in Fig. 1, two months later and after irradiation.

moved for microscopic examination. Dr. A. C. Broders, who examined the tissue, reported adenocarcinoma, Grade 4. A small lymph gland was excised from the left inguinal region and a pathologic report of tuberculous adenitis was made.

On April 4, 1936, treatment with radium was begun. Twenty-nine 1.0 mg. needles, with a filtration of 0.5 mm. of platinum, were applied to the growth interstitially. This treatment extended over a period of four days and a dose of 2,374-mg. hr. was given. There was marked regression of the lesion during this time. Between April 17, 1936, and July 7, 1936, the patient was given deep x-ray therapy to the pelvis, totaling 4,200 r. Two months after the beginning of treatment there was no evidence of the growth. She was discharged from the hospital on July 27, 1936.

The patient returned to the hospital in October, 1936, several months after the treatment with radium. At this time there was a small area of recurrence, measuring slightly over a square centimeter, on the posterior vaginal wall, midway between the introitus and the cervix.

This area was treated with interstitial radium, a total of 133 mg. hr. being given. This radium treatment was followed by further x-ray treatment, 2,400 r. being given. The mass previously palpated deep in the left side of the pelvis had increased in size. Following the second series of treatments the patient developed a painful area of radio-neerosis about the vulva and lower vagina. This condition was improving when she was discharged from the hospital on Feb. 9, 1937, with chickenpox.

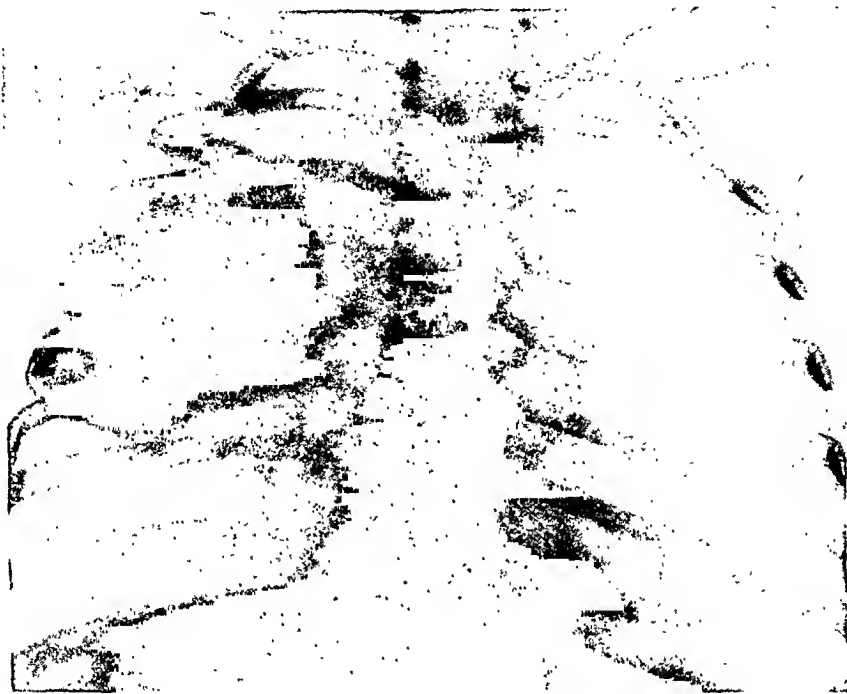


Fig. 4.—X-ray of chest, one year after Fig. 1, showing metastasis.

On March 26, 1937, she returned to the hospital acutely ill. The area of necrosis was smaller. No carcinoma was apparent on the vulva or in the vagina. The left leg was swollen and cyanotic throughout. It appeared several times as large as the right leg. Her temperature was 104° F.; her respirations and pulse were very rapid. X-ray examination of the chest at that time showed an oval density practically filling the upper two-thirds of the right lung. This was diagnosed metastatic carcinoma. X-ray therapy was given. The enlargement of the left lower extremity was believed to be due to obstruction by the mass deep in the left side of the pelvis. The patient continued to be very weak and seemed to suffer pain. She developed a cough and dilatation of the veins of the head and neck. Her condition continued to progress unfavorably and she was discharged from the hospital on May 24, 1937, at the request of her parents. She died at home on June 17, 1937, at the age of three. Death occurred fourteen months after the first treatment. Autopsy was not performed.

Summary and Conclusion

Carcinoma of the female external genitals in infants is very rare. A case of adenocarcinoma involving the vulva and the lowermost part of the

vagina is reported. Signs of the disease appeared when the child was five months old. A visible external lesion appeared when the patient was sixteen months old. Microscopic diagnosis was made when the child was twenty-one months old. This is one of the youngest cases, possibly the youngest case, of carcinoma in this site yet to be recorded in the literature.

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HYPERNEPHROMA OF THE OVARY

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THE patient, a 52-year-old white woman, was admitted to Lincoln Hospital on Nov. 27, 1940, with the complaint of abdominal pain and cramps for twenty-four hours. She had been in her usual health, attending to her duties as a housewife until the day before when the above symptoms began. They were at first interpreted as an attack of biliary colic, similar to those from which the patient had suffered for many years. In twelve hours she had become weak and irrational. On admission she was in shock and stuporous. Pulse and blood pressure were not obtainable; heart sounds were poor. Temperature was 98° F. The abdomen was distended and tender. A large mass was present in the abdomen, nearly filling the left side which was dull to percussion. No evidence of free fluid was obtained. Pelvic examination revealed tenderness in the left pelvis but no intrapelvic mass. Urine revealed an occasional granular and hyaline cast. A bedside x-ray showed no free air in the abdomen.

The abdominal findings were interpreted as a possible acute diverticulitis with perforation. The patient was transfused but became weaker, comatose, and died eight hours after admission, approximately thirty hours after the onset of acute symptoms.

The past history revealed 2 normal full-term pregnancies and deliveries, the last 20 years ago. Since then the patient had suffered from occasional nocturnal attacks of typical biliary colic, but these passed within a few hours and she had never been jaundiced.

However, the significant part of the past history was that in 1929 she had developed severe hematuria and a diagnosis of renal tumor had

been made at another hospital. On Sept. 19, 1929, the right kidney was removed through a lumbar incision. It was found to contain a tumor "in its upper two-thirds, entirely within the substance of the kidney," measuring 8 by 10 by 5 cm. At no point had the tumor ruptured outside of the capsule of the kidney; it was entirely encapsulated. It had not extended into the ureter, renal artery, or vein (no mention is made of whether it extended into a calyx) and showed the typical appearance of a hypernephroma with a yellow appearance in places and a large gelatinous-like area of degeneration in the center and in other places a few small hemorrhages.



Fig. 1.—Uterus, posterior view, showing solid tumor attached to broad and round ligaments. A large thin-walled cyst is attached to the tumor.

Slides were no longer available but the microscopic report at the time read "... The tumor is a hypernephroma with areas of mucoid degeneration. It is definitely separated from the renal parenchyma by a fibrous capsule. Some small areas of hemorrhage and areas of edema. The pelvis is not involved and no large vessels are seen thrombosed by the tumor. Diagnosis: Hypernephroma of the kidney."

In 1931, the patient had a conization of the cervix for erosion and laceration. She had a natural menopause four years before the present illness and no vaginal bleeding since.

Autopsy

External Examination.—The body was that of a moderately obese middle-aged woman of normal habitus. No hirsutism was present. The external genitals were normal for the age. A left oblique lumbar scar was present.

Abdominal Cavity.—The abdominal cavity contained approximately 2,500 c.c. of blood, about 1,200 c.c. being clotted. In the left iliac fossa was a thin-walled cyst approximately 18 cm. in diameter. This was contiguous to and connected by a fibrous band with a smaller, ruptured cyst about 8 cm. in diameter, filled with clotted blood. The latter was attached to the broad and round ligaments of the uterus and lay about 10 cm. from the left cornu in the pelvis. On its posterior and medial (tubal) aspect was a bright yellow-orange solid irregular, somewhat loculated mass (ovarian tumor) approximately 3.5 by 3.5 by 4 cm. in size.

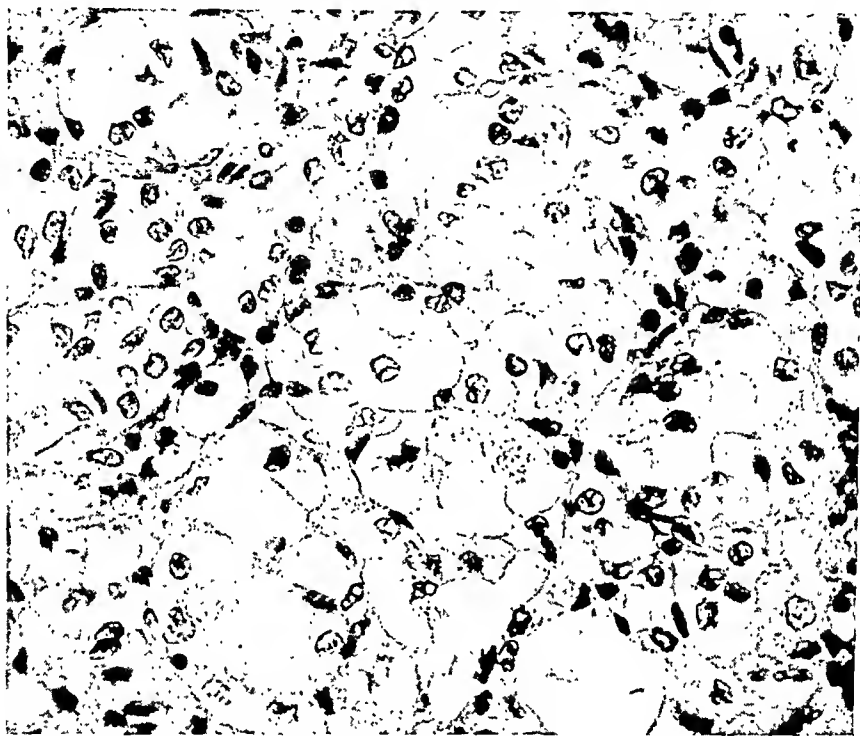


Fig. 2.—Section of ovarian tumor showing clear and granular cells with small round nuclei and thin reticulum.

This mass grew into and formed part of the cyst wall, spreading out for a short distance in plaque form on its inner surface. Section showed the tumor to have a moderately variegated appearance. Some areas consisted of homogeneous orange-yellow tissue containing a few small cysts. Other areas, especially those growing into the cyst, contained large, dilated blood-filled spaces, apparently channels, one of which, about 4 mm. in diameter, opened into the cyst and appeared to have been the site of bleeding. The rest of the cyst wall was smooth, thin, and translucent. There was no grossly identifiable ovarian tissue on the left side. The cysts and mass seemed to bear the relationship, though distorted, of the left ovary. The large cyst contained a clear, thin, light yellow fluid and was lined by a translucent membrane. The tubes, uterus, and right ovary were atrophic.

The right kidney was absent. The left was essentially normal.

Microscopic Examination.—The fleshier parts of the tumor showed closely packed alveoli, clearly shown by Bielschowsky stain to be surrounded by a thin reticulum, continuous from alveolus to alveolus. The

latter consisted of 8 to 12 large, polyhedral, or rounded cells with clear or granular eosinophilic cytoplasm, and small round or oval, for the most part dark, centrally located nuclei, without nucleoli. Occasional nuclei were moderately vesicular. Many were eccentric, even peripheral. An occasional cell appeared multinucleated, but no bizarre or giant forms were seen. No mitoses were noted. Occasionally there were transitions to tubules or acini lined by a single layer of cuboidal cells similar in other respects to the cells of the alveoli. The clear cell alveoli were present in clusters surrounded by groups of granular-cell alveoli. The latter cells were smaller. In the vascular parts were channels of all sizes consisting of an endothelial layer with little or no surrounding connective tissue. Some of the channels were enormous. In these areas columns and clumps of cells were outlined by vascular channels. Here and there the vascularity was so great and the channels so closely approximated as to leave no intervening tumor cells, but merely narrow bands of collagen. Cystic spaces of various sizes lined by flattened elongated cells and filled with homogeneous pink-stained material were seen in many sections. Necrosis was minimal. Occasional hemorrhagic areas were noted. Scarlet R stain showed the presence of large amounts of fat, filling many tumor cells completely and present, at least as granules, in most. Only a rare droplet stained pink with Nile blue sulfate, the rest staining blue green. No doubly refractile material was seen.

Discussion

We are inclined to regard the ovarian tumor in this case as a metastasis from the renal neoplasm. This opinion is based on the characteristic histology and the clinical history.

The histology is identical with the so-called Grawitz or hypernephroma type, which according to some authors arises from an adrenal rest in the kidney. Others (Stoerk, Schiller) believe this tumor is of renal tubular origin or arises from a "rest" of embryonal renal tissue within the kidney (Wilson and Willis, Geschickter). Most authors believe that the characteristic "clear-cell" variety is a more differentiated, less malignant type than the "granular-cell" kind. Although some prefer to call the former hypernephroma and the latter adenocarcinoma, it becomes more and more apparent that they are genetically identical and that the distinction is of value for clinical prognostic purposes only (Fouldes and Braasch, Hunt and Hager, Geschickter). Actually both granular and clear cells, alveolar and papillary formations, are present in most of these tumors, although one or the other may predominate (Bonnar, Geschickter). In our case, cell structure was both clear and granular. Structure was chiefly alveolar, although a papillary appearance was present in one area. There was a distinct tendency to tubule formation which is characteristic of the renal hypernephroma (Geschickter, Schiller, and others). The presence of large, thin-walled blood sinuses is another suggestive feature. Primary hypernephroid ovarian tumors appear, from descriptions and illustrations, to be more uniform in structure, without tubule formation and not as vascular as the renal tumors or the one described here. According to Greenblatt and others primary ovarian hypernephroma contains crystalline doubly refractile and metachromatic (with Nile blue sulfate) droplets similar to those found otherwise only in adrenal adenomas and different from the pattern in renal hypernephroma. This we could not confirm. However, although this may

suggest that this tumor did not arise from an ovarian adrenal rest, it does not prove that it arose from a renal hypernephroma. Unfortunately, we were not able to obtain sections of the original renal tumor, but from the description there is no reason to doubt that it was a typical Grawitz tumor. Although eleven years may be considered a rather long interval for such a small metastatic tumor to manifest itself, especially in such an indirect manner, behavior of this type is almost characteristic of certain cases of hypernephroma.

Summary

1. Hypernephroid tumors, i.e., yellow tumors containing large lipid filled cells, of the ovary have been described over the course of many years. The tumors differ considerably in appearance and behavior. Some have been masculinizing; a few have produced precocious puberty. There has been and still is much discussion about the histogenesis of these tumors, some favoring an adrenal rest; some a lutein cell origin. There are many contradictions in each point of view, and great confusion about these tumors still exists. It is highly questionable if they do constitute a definitive group.

2. A case of such a tumor is presented, which is believed to have been secondary to a renal hypernephroma removed eleven years before. The ovarian tumor bled into a large serous cyst of the ovary and caused fatal intraperitoneal hemorrhage.

3. Renal hypernephromas and their metastases are bizarre in their behavior. Long time-intervals and peculiar manifestations from the metastases have been the subject of many papers. Ovarian metastases are very rare. This case constitutes the third, or possibly the fourth, on record.

Moore, John H.: The Late Effects of the Toxemia of Pregnancy, *Journal-Lancet* 61: 368, 1941.

The author reports his results after following 57 patients who could be classed as toxemias of pregnancy. He found only two diseases that appeared noteworthy in favoring the development of a toxemia of pregnancy and those were scarlet fever and recurrent tonsillitis. These diseases either alone or together were noted in 57 per cent of these cases. Fifty-nine per cent of the toxemias occurred in primiparous women. Ten premature and three full-term infants born to mothers with nephritic toxemia survived, a salvage rate of approximately 50 per cent; 20 infants (4 premature and 16 full term) born to mothers with pre-eclamptic toxemia survived including one set of twins, or a salvage rate of almost 87 per cent. Eight of the nine babies born to eclamptic mothers, or 88 per cent, survived. The incidence of twins in these groups was 5 per cent.

In 19 patients with a nephritic type of toxemia, there was a survival of 12 infants in 29 subsequent pregnancies. In 13 patients of the original group of 23 who were diagnosed as pre-eclamptic toxemia seven showed evidence of nephritis in subsequent pregnancies, four had questionable cardiorenal vascular disease, and only two had no untoward symptoms or incidents to mar their subsequent pregnancies. The pre-eclamptic and the eclamptic group, while they showed no mortality, gave evidence of recurrent toxemia or of permanent cardiovascular renal changes in 83 per cent of the cases in subsequent pregnancies.

WILLIAM BERMAN.

BILATERAL MICROCYSTIC DEGENERATION OF THE OVARIES AND MASCULINIZING SYNDROME

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EXTENSIVE masculinization in association with microcystic disease of the ovaries is a very uncommon condition. Two cases of this syndrome recently reported by Geist and Gaines² displayed a bilateral follicular degeneration of the ovaries with striking proliferation and luteinization of the theca interna. Numerous clusters of luteinized cells were also found throughout the ovarian stroma. The cases described had both ovaries removed. One of the patients who was followed showed no evidence of clinical improvement after operation.

Stein, Leventhal and Robinson³⁻⁵ obtained gratifying results by resecting polycystic ovaries in patients with amenorrhea and sterility. Normal menstruation was re-established in almost all of their cases. Some of the patients became pregnant and gave birth to normal living children. The ovarian tissue was described as having a thick tunica with numerous cysts of varying size lined mostly by an hypertrophied thecal layer with scarce granulosa cells.

The following case showed pathologic and clinical changes which were quite similar to those found by Geist and Gaines.² A different end result was obtained, however, by resecting instead of removing both ovaries.

Case Report

A. S. (History No. 103829), single, 23-year-old factory worker, presented herself on Aug. 20, 1940, complaining of amenorrhea and growth of hair on the face and abdomen of six months' duration. The hirsutism became very pronounced and she tired easily during the past two months. No significant facts were elicited from her family or past history except that her mother was a diabetic. Her menses began at 14 years, four to seven weeks' interval, four to five days' duration, moderate flow without associated symptoms. The last menstrual period occurred in February, 1940.

Examination revealed a moderately obese 23-year-old white female, appearing very nervous but not acutely ill. Temperature was 98.6° F.; pulse, 96; blood pressure 132/80. The chin had a luxurious growth of thick blond hair in spite of the fact that she had shaved within a few days. The breasts were smaller than expected in an obese female of her size. The heart, lungs, and abdomen were normal. Pelvic examination, which was done under anesthesia, revealed a masculine type escutcheon, an atrophic labia majora and minora, an hypertrophied clitoris to 2.5 cm. in length, a narrow vagina admitting two fingers with difficulty, and a very narrow short cervix with a pin-point orifice. The corpus uteri was double the size of the cervix but also very small. Both ovaries were readily palpable. The right ovary seemed to be larger than the corpus uteri. The left ovary was smaller. The Fallopian tubes were not palpable.

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X-ray examination of the sella turcica was negative. X-ray visualization after injection of air into the suprarenal spaces revealed no evidence of adrenal enlargement. There was a slight trace of albumin in the urine. The blood Kahn was negative. A complete blood count and blood chemistry was found to be within normal limits. The basal metabolic rate was plus 8.



Fig. 1.—Low-power section of the ovary showing cystic follicular degeneration with marked density of the ovarian stroma.

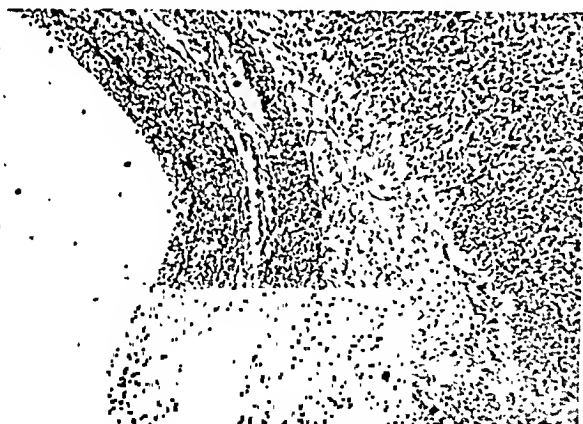


Fig. 2.—High-power section presenting a narrow well-defined granulosa layer, a wider well-developed luteinized theca interna, and a cluster of lutein-like cells within the ovarian stroma at some distance from the follicle.

The preoperative diagnosis was masculinizing tumor of the right ovary. A dilatation and curettage and a laparotomy through a midline incision was done. A very small amount of endometrium was obtained. The uterine cavity was only 1 cm. in length. Both ovaries were studded with small follicular cysts. The right ovary was almost twice the size of the corpus uteri and the left ovary was almost as large as the corpus uteri, which measured about 4 by 2 by 2 cm. The Fallopian tubes were normal. An incision into both ovaries disclosed widely scattered follicular cysts throughout the cortical tissue. The cysts contained a clear mucinous fluid. Two-thirds of each ovary was resected and the remaining cysts were carefully punctured and emptied. Both adrenals were

palpated through the abdominal cavity and were found to be of normal size. The appendix was removed and the abdomen closed.

Microscopic study of several regions of the available ovarian tissue disclosed no evidence of an androgenic tumor. The follicles were cystic and widely scattered throughout the cortex. Most of the follicular walls contained a well-defined narrow granulosa layer with a much wider well-developed theca interna showing distinct luteinizing characteristics. The stroma was dense and contained clusters of luteinlike cells at some distance from the follicles. The endometrial glands were small, poorly defined, with a tendency toward secretory activity; the intervening stroma contained a large number of red blood cells.



Fig. 3.



Fig. 4.

Fig. 3.—Endometrium obtained during the operation showing marked atrophy with poorly defined small glands and a tendency toward secretory activity.

Fig. 4.—Endometrium obtained about sixteen months after operation during the twentieth day of the cycle showing an abundant amount of endometrium in a well-developed proliferative phase with some evidence of secretory activity.

The patient left the hospital on the tenth day after operation. A normal menstrual flow of seven days' duration occurred in four weeks and has been recurring periodically every twenty-eight to thirty days. No additional evidence of hirsutism appeared after the existing hair was removed by electrolysis. The breasts have become larger and normal in appearance. The hair on the abdomen has almost completely disappeared, and the escutcheon hair has become characteristically female. An endometrial biopsy was done twenty days in the cycle about sixteen months after operation and an adequate amount of endometrium was obtained. Microscopic study revealed a well-developed proliferative phase with some evidence of secretory activity. The uterine cavity measured 6 cm. in length and the uterus seemed to be normal in size.

Comment

Our present-day knowledge of endocrinology does not explain the exact mechanism which causes the masculinization syndrome in the presence of luteinized microcystic degeneration of the ovaries.

Geist and Gaines² are of the opinion that the ovarian changes are incidental findings with the masculinizing syndrome. The case which they observed after operation did not improve even after both ovaries were removed. They also quote Bergstrand who had a case similar to theirs which revealed a basophilic adenoma of the pituitary and a diffuse hyperplasia of both adrenal glands at autopsy. They, therefore, concluded that the syndrome was primarily caused by pituitary basophilism or adrenal cortical lesions. The end result in my patient does not bear out their contention. Since no recurrence of symptoms was noted when she was last seen about two years after operation, it is safe to infer that the pathologic changes in the ovaries were the primary factor for the syndrome.

No facilities for blood and urine hormone determinations were available at the time. The evidence of secretory activity of the atrophic endometrium and the marked luteinizing changes of the ovaries would tend to support the possibility that a large amount of progesterone was present in the body. Perhaps the masculinizing changes which occurred here may have been associated with or due to an excess amount of progesterone as one frequently sees in cases of adrenal cortex neoplasms.^{1, 6, 7} Resection of the ovaries apparently re-established a normal endocrine balance with a very good clinical result.

Summary and Conclusions

1. The case presented had a far-advanced masculinizing syndrome which was associated with microcystic degeneration of the ovaries, a marked luteinization of the theca interna, and some luteinization of the ovarian stroma.

2. Resection of two-thirds of each ovary and puncture of the available cysts resulted in restoration of regular periodic menstruation, growth of the uterus to the usual normal size, decrease in the size of the clitoris, enlargement of the breasts, and cessation of the growth of hair on the face and abdomen.

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HYDATIDIFORM MOLE IN A TWIN PREGNANCY, WITH A PREMATURE LIVING INFANT

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THE finding of hydatid changes of varying degrees in early pregnancy in association with pathologic or so-called blighted ova is common. Meyer⁸ in his work on specimens in the Mall collection found that about one-third of uterine abortions showed definite molar degeneration. He calculated that at least 10 per cent of all conceptions end in hydatid degeneration, thus making it one of the most common diseases of the placenta and fetus during the early months of gestation. However as pregnancy approaches term such changes are progressively more uncommon, or even rare.

Cases of typical hydatidiform moles coexisting with a well-developed fetus occasionally have been reported. As Bland² points out, the existence of a well-developed fetus and an advanced mole in the uterus at the same time would seem physically impossible except in a plural pregnancy. The suggestion of a twin pregnancy is even more striking in those cases in which the primary expulsion of a fetus with membranes and placental tissue is followed several hours later by the expulsion of a mole. However, the simultaneous expulsion of mole and fetus has likewise been observed.

There are numerous reports of such cases in the literature. Brews⁴ had two cases of twin pregnancy each with a normal fetus of about fourteen weeks coexisting with a hydatidiform mole. Kangas,⁶ Meyer,⁸ Speiser,⁹ Strauch,¹⁰ among others, have published similar records.

Clinical reports of live normal infants associated with a hydatidiform mole, as seen in the present case, are few. In recent years Beasley,¹ and Favreau and Belanger,⁵ have reported cases of a normal infant at term with a typical mole.

Report of Case.—Mrs. M. S., a white woman, 24 years of age, history No. 37250, was a nonclinic gravida ii, whose last menstrual period was July 20, 1938, and the expected date of confinement April 27, 1939. Her prenatal course had been apparently uneventful. She was admitted on March 28, 1939, in labor with a history of a moderate bloody show for the previous two hours. Her bag of waters had ruptured just prior to the onset of pains.

Her previous pregnancy had been entirely normal with a natural delivery of a normal full-term infant at home. The patient's health had always been good except for childhood diseases.

Physical examination revealed a well-developed and well-nourished woman in early labor. Blood pressure was 130 systolic, 80 diastolic, pulse rate was 112 per minute, and temperature 99.2° F. The uterus was symmetrically enlarged, reaching to just above the umbilicus and was slightly tender. Fetal parts could be palpated and the fetal heart was audible in the right lower quadrant, rate 156, and of good quality; cephalic presentation. Because of a rather profuse bloody

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show, rectal examination was deferred. Diagnosis was pregnancy at thirty-six weeks, with possible placenta previa.

Patient was taken immediately to the delivery room, where labor progressed very rapidly. On vaginal examination the cervix was found to be fully dilated, and the vagina contained considerable free blood. A rather small infant was delivered spontaneously, occiput right anterior, following a few uterine contractions.

Search for the source of the bleeding was made immediately. A disc-shaped mass resembling a placenta without cord was found in the vagina, and it delivered spontaneously. On the posterior lip of the internal os was a firm mass, apparently a small intramural fibromyoma, which pushed the internal os upward, the whole projecting through the internal os. This was pushed up manually and the cervix plicated at the sides with chromic catgut to maintain it.

The placenta was expelled intact after a third stage of ten minutes and following this 1 c.c. of ergometrine was administered intramuscularly. Total blood loss was estimated at 400 c.c. from the time of admission.

The infant breathed spontaneously, had a vigorous cry, and weighed 2,150 Gm. A thorough examination revealed no abnormalities. She was placed in the premature nursery, had an uneventful neonatal course, and was discharged on the forty-first day weighing 3,000 Gm.

The mother had a normal post-partum period. Following an initially positive Aschheim-Zondek test twenty-four hours post partum, all further tests have been negative. When last contacted two years following delivery, she had had no further pregnancies and her Aschheim-Zondek test was negative.

The pathologist, Dr. Nicholas M. Alter, reported as follows:

Specimens consisted of two placentas. The first weighed 435 Gm. and was 17 by 15 by 3 cm. The cord was eccentrically inserted and rather long. The fetal surface was smooth and the maternal surface showed only a few irregular opaque white spots varying from 1 to 3 m.m. in diameter. Microscopic sections showed thin villi with well-developed and slightly congested blood vessels. They were covered by thin atrophic chorionic epithelium. The diagnosis was normal placenta. The second placenta-like mass weighed 475 Gm. and had approximately the same measurements. There was no evidence of a cord. Fetal membranes were present, but there was no evidence of a fetus. The fetal surface was quite pale and obviously thickened. The decidua surface was irregular, nodular, and uneven. Within torn areas cystic structures were seen having varying diameters. Numerous cross sections through the mass revealed very little solid tissue. Microscopic sections showed cystic villi with fibrosis. No normal villi or blood vessels were seen. The tissue was made up of cystic structures some of which were filled with dark-celled myxomatous tissue and covered by moderately hyperplastic chorionic epithelium. Diagnosis was hydatidiform mole.

Discussion

An unusual case of a hydatidiform mole occurring in a twin pregnancy with a premature living infant is reported. The importance of the phenomenon other than its obscurity is the opportunity given to emphasize again the need for follow-up in all such cases of twin pregnancy as possible sources of a later chorionepithelioma. Matthieu and Palmer⁷ reported a case with a three months' fetus in which there

developed a chorionepithelioma two months afterward. In a similar case, Bland² depicted the transition of a benign hydatidiform mole to a perforating or malignant mole and finally to a highly malignant chorionepithelioma. The clinical diagnosis of an abortion may seem correct and obvious with a fetus alone, and the true diagnosis of hydatidiform mole thus be obscured. Brews³ reported three cases of chorionepithelioma following abortions which "may have been hydatidiform moles" by clinical history, but not confirmed by pathologic study.

The fact that such a case as the one here reported can occur would seem to strengthen the hypothesis that hydatid mole originates as the result of some intrinsic abnormality of the ovum, rather than one present in the harboring maternal structures.

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39 GIFFORD AVENUE.

DOUBLE MONSTER, PYGOPAGUS

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(*From the Obstetrical Service of the Good Samaritan Hospital*)

THIS 24-year-old white woman was admitted to the Good Samaritan Hospital on Oct. 11, 1942. Her last menstrual period had been on Jan. 28, 1942, making her delivery due November 4. Her past medical history was essentially negative. She had had one previous pregnancy in 1940, which had gone to term, and she had a spontaneous delivery of a viable child weighing 8 pounds 7 ounces after a six-hour labor. She had a post-partum hemorrhage and was given three transfusions.

This pregnancy had been uneventful up to the time of admission. Wassermann and Kahn tests were negative. Urinalysis had been negative and blood pressure on admission was 98 systolic and 64 diastolic. Contractions had started a short time before coming to the hospital and the membranes had ruptured. The abdomen was large and two fetal hearts could be heard. About an hour after admission two feet presented at the vulva and she was taken to the delivery room. An unsuccessful attempt at breech extraction was made. Trying to determine the cause of the dystocia a hand was inserted into the uterus and another foot could be felt which seemed to be smaller than the two presenting. It was assumed that the second twin was in some way interfering with the delivery of the first but the true condition was not recognized. Two fetal hearts could still be heard, so it was decided to perform a cesarean section. A classical section was done and the monster delivered through a long incision in the uterus. The patient bled considerably, due to the overdistention of the uterus, but was in pretty good condition on return to her room. A transfusion was given on the third day. She showed no

signs of infection and had a smooth convalescence, leaving the hospital on the eleventh day.

At the time of delivery the baby on the right, designated as "A," started crying and had a good color. The baby on the left, designated as "B," was cyanotic and appeared lifeless. About two hours after birth, B started breathing and its color improved, but was never as good as that of A. Both babies were hydrocephalic. There was one cord which went to A. B had the remnants of an umbilicus and a stringlike cord about three inches long. The monster weighed eleven pounds and



Fig. 1.

twelve ounces. B had a cleft palate. The babies were fused at the sacrum. There were one anus and one external genital which were edematous and dark in color. The two legs and feet forward were of the same size and were loosely connected to the body. From the position of the great toes apparently one of these two extremities belonged to each baby despite the difference in size between them and the other two extremities which were of the same size and were the two presenting. They voided and passed meconium normally.

The placenta was large and had only the one cord which went to A.

The monster lived for forty-eight hours. Autopsy showed the organs above the diaphragm normal in appearance. Livers and spleen appeared

normal. Each fetus had a right kidney but none on the left side. A had one adrenal gland and B had two. The intestinal tracts opened into a common cloaca just above the common anus. Each had a uterus, tubes, and ovaries. Each had a vagina that opened between the common



Fig. 2.

labia. None of the organs were opened because the parents had agreed to give the specimen to the University for further study. Later they changed their minds and carried out a burial.

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200 WEST SECOND STREET

VITAMIN B FACTORS IN TOXIC PSYCHOSIS OF PREGNANCY AND THE PUERPERIUM

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FROM experience with two cases it appears that psychosis in pregnancy and the puerperium may in some cases be associated with disturbances in vitamin B metabolism.

Last year, at the Louisville General Hospital, a patient was admitted with pernicious nausea and vomiting of pregnancy. She received the usual therapy, consisting of intravenous fluids and small dry feedings for a period of two weeks. At the end of that time she had developed neuritis, reddened tongue, and a psychosis. Moderately large doses of vitamin B components: 100 mg. of thiamin chloride, 100 mg. of niacin, 50 mg. of pyridoxine hydrochloride, 50 mg. of pantothenic acid, and 10 mg. of riboflavin were given intravenously each day for three days. At the end of that time the nausea was gone, the neuritis improved, and the psychosis was better. Intense therapy was continued orally and by the end of a week all symptoms disappeared. She went to term and delivered normally. Since psychosis is often associated with niacin deficiency, it was assumed that hers was likely on this basis.

More recently a private patient, who had developed eclampsia and was treated conservatively by her family physician until the convulsion ceased, was referred to Dr. McConnell who delivered her by cesarean section. The postoperative course went smoothly until about thirty-six hours at which time the nurses met her in the hall. She said, "My room is full of soldier boys and blue lights are flashing from the fixtures." She was put to bed and kept there only by the constant attendance of a nurse.

On the basis of the previous experience we decided to give nicotinamide and thiamin chloride in large doses. She received 300 mg. of each intravenously in divided doses during the first twelve hours and a total of 900 mg. of each over seventy-two hours. Within twenty-four hours her mental condition had cleared. The medication was discontinued after three days. There was no recurrence of her symptoms.

Neither of these patients had any insanity or other nervous diseases in the family background. Both of them had had clear-cut toxic disturbances before the onset of the psychosis. This mode of therapy seems worthy of further trial.

It would also be interesting to try this treatment on those patients who develop psychosis comment after severe infections.

Two patients who developed psychosis after toxic disturbances in pregnancy responded to therapy with vitamin B components. The niacin was probably the most important factor.

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INVERSION AND PROLAPSE OF A RUPTURED UTERUS DURING LABOR, TREATED BY IMMEDIATE VAGINAL HYSTERECTOMY*

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THIS case is reported because of the unusual sequence of events and the successful treatment.

Mrs. X., aged 42 years, gravida vi, para v, entered the West Suburban Hospital at 2:30 P.M., August 31, 1942. She was at term but not in labor. Examination was essentially negative except that the patient was very obese, weighing about 190 pounds. Diagnosis of transverse presentation was made by the attending physician.

Past obstetrical history was as follows: First pregnancy, normal delivery, 10-pound boy, November, 1923; second pregnancy, normal delivery, 6-pound girl, December, 1925; third pregnancy, forceps delivery, 10½-pound boy, stillborn March, 1936 (patient was in labor two days before this delivery); fourth pregnancy, forceps delivery of a stillborn 10-pound girl (patient had premature rupture of the membranes about two weeks before and had high fever following this delivery); fifth pregnancy, normal delivery, 7-pound girl, May, 1939. She was five days past the date of expected confinement with her sixth pregnancy. Last regular period, Nov. 18, 1941: Expected date of confinement, Aug. 26, 1942. Her prenatal course was uneventful but since she did not go into labor at the expected time, and because of the history of large stillborn babies, the attending physician sent her into the hospital for induction of labor.

At 9:00 P.M., August 31, labor was induced with castor oil and quinine. Mild pains started promptly and the membranes ruptured spontaneously at 11:30 P.M. Mild labor continued through the night.

At 9:30 A.M. September 1, a large amount of meconium was passed. Vaginal examination at 10:00 A.M. disclosed a frank breech presentation. The cervix was 4 cm. dilated and the breech was at station minus one. Fetal heart tones were slightly irregular. The patient was having mild labor pains.

At 10:15 A.M. the attending physician ordered pituitrin minims 2. This was repeated at 10:30 and again at 11:15, making a total of 6 minims of pituitrin in one hour.

At 11:30, fifteen minutes after the last dose, the patient complained of excruciating pain in the left lower abdomen and began to have frank vaginal bleeding. There was no evidence of shock. This pain lasted about ten minutes and then gradually subsided. At this time the fetal heart tones became irregular and were not heard after 11:45 A.M.

At 12:00 noon another vaginal examination was made by the attending physician and at this time he could not feel the presenting part. The first consultant was then called in. Examination by this consultant showed that the cervix was fully dilated and that a boggy mass, which he thought to be an ablatio placenta, filled the cervix. He then noted that his hand was apparently inside the abdominal cavity and

*Presented at a meeting of the Chicago Gynecological Society, November 20, 1942.

that the fetus was in the uterus to the right of his hand and in an oblique position. He was able to bring down the anterior leg and then to extract a stillborn, 8½ pound boy.

Unsuccessful attempts were then made to express the placenta and a manual removal was attempted. During this procedure the uterus suddenly became inverted and delivered outside the vulva. Evidently the torn edge of the uterus was mistaken for the placenta and traction on it inverted the corpus through the rupture in the lower uterine segment. The placenta was not attached to the uterus but remained inside the abdomen. The consultant immediately corrected the inversion by turning the corpus right side out through the torn area. He was unable to replace the uterus in the pelvic cavity.

The second consultant was then called and found a complete extraperitoneal prolapse of the fundus with both tubes, both round ligaments and the left ovary visible. There was a large tear in the left lower uterine segment extending from the left round ligament down to the cervix. The cord was protruding through the vagina below the uterus. The patient's condition was fair but she was continually losing blood.

The only method of treatment that seemed at all reasonable or possible under these circumstances was to do an immediate vaginal hysterectomy. This was easily accomplished by starting from the fundus and working down toward the cervix. Both broad ligaments, including the tubes and round ligaments, were clamped and ligated. When the area of the lower uterine segment was reached, the bulk of the fundus was amputated. This gave access to the anterior vaginal wall which was now reflected, followed by the reflection of the bladder. The parametria were then clamped and ligated and the remainder of the uterus removed. A tight pack was inserted into the opening in the vaginal vault and the entire vagina was tightly packed. Before doing the hysterectomy, the placenta was found to be free in the pelvic cavity and was easily removed.

The patient had all of the usual restorative measures, including plasma, glucose solution and whole blood intravenously, which were started soon after the patient showed signs of ruptured uterus. She also received large doses of sulfathiazole. Her convalescence was remarkably smooth. During the first two days she had marked abdominal distention, which responded promptly to prostigmin and enemas. Her temperature at no time went above 101° F. The vaginal pack was removed in 24 hours and there was no further bleeding. The patient left the hospital on the 14th postoperative day.

This case again illustrates the danger of using even small doses of pituitrin during labor especially in a questionable presentation. It also presents an unusual cause for inversion of the uterus. Apparently the tear in the uterine wall was mistaken for the placenta and as it was being pulled down for inspection the uterus suddenly inverted.

Vaginal hysterectomy was the only feasible method of dealing with these complications. The fact that in this case, the presence of a large tear in the uterus made it possible to correct the inversion and perform a vaginal hysterectomy, suggests the possibility of treating inversion by making an incision in the uterus to correct the inversion and following this by vaginal hysterectomy. This procedure may be worthy of trial in certain selected cases.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

AN EVALUATION OF THE METHODS FOR TREATING NON-MALIGNANT UTERINE BLEEDING IN THE MENOPAUSE

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THE choice between hysterectomy and irradiation castration for the control of benign menopausal bleeding from the normal-sized uterus, the fibrous uterus, or that associated with myomas must be governed by several factors. Questions which must be answered before a decision as to type of treatment is made are: (1) are the two methods comparable in effectiveness? (2) is the associated morbidity and mortality appreciably higher for either of the procedures? (3) is the incidence of uterine carcinoma following irradiation high enough to be a distinct hazard? and (4) is either method of treatment contraindicated for any individual patient? In the following discussion an attempt will be made to evaluate the methods of treating this selected group of patients.

Indications and Contraindications

In general the contraindications for either of the two methods of treatment may be used as an indication for the other. The patients in whom the removal of the uterus is contraindicated are those who are poor risks for any major surgical procedure. Included in this group are the obese individuals in whom operation would be hazardous and difficult, those with degenerative diseases such as diabetes and cardiovascular renal disease, those with blood dyscrasias, and the aged individual whose life expectancy is short.

The upper limits of uterine size usually considered acceptable for radium treatment is that comparable to a ten to twelve weeks' gestation. Deep x-ray therapy may be used effectively in this size tumor as well as in those which are much larger; in the latter, however, operative removal is usually a preferable procedure. The primary effect of both x-ray and radium is the inhibition of ovarian function. The latter, however, also produces sclerosis of the endometrium which aids in stopping the bleeding. Thus the insertion of radium in the larger myomas may fail to control bleeding completely because the large cavity and the thick uterine wall increase the distance from the source of radiation to a point at which the ovaries are not effectively irradiated.

Enlarged uteri producing symptoms other than bleeding should be removed if possible since treatment by castration, while it may stop bleeding, does nothing to relieve the associated symptomatology. Most enlarged uteri become smaller after cessation of ovarian function, but the amount of regression and the extent to which the symptoms will be relieved cannot be predicted. Degenerated fibroids obviously are best

treated by surgical removal. Since the bleeding from pedunculated submucous myomas often is from actual destruction of the tumor rather than from the endometrium the insertion of radium may, in some cases, increase the necrosis in the neoplasms and exaggerate rather than relieve the symptoms. If the endometrium over a submucous myoma is very thin, the destruction from the radium may be followed by local infection and occasionally sepsis. Pedunculated subserous fibroids may degenerate following irradiation as a result of a decrease in available blood supply and are best treated surgically.

Patients who have had either previous pelvic surgery or pelvic inflammatory disease often are not good candidates for irradiation. Loops of bowel which may have become adherent in the pelvis are likely to receive destructive doses of radiation resulting in stricture, and quiescent inflammatory processes may be activated. The palpation of adnexal masses contraindicates radiation therapy because of the impossibility of diagnosing accurately the type and extent of the pathology present by bimanual examination alone.

The common association of x-ray or radium with the treatment of malignant tumors may, as a purely psychologic measure, be an indication for hysterectomy. Irradiation, if forced upon the patient, may be followed by undesirable mental reactions even though the result of therapy be perfect.

Age of the patient must be one of the primary considerations before a plan of therapy is outlined. Since both radium and x-ray therapy destroy ovarian function, neither is the treatment of choice for the younger individual in whom the uterus can be removed and the ovaries, if normal, retained. Taussig sets the lower age limit for irradiation at 42, but in certain patients in whom menopausal symptoms are already present irradiation may be justifiable earlier.

Technique of Irradiation

The desired effect, castration with control of the bleeding, may be accomplished satisfactorily by adequate dosages of either radium or deep x-ray therapy. Brown and others have demonstrated that the lower the total dosage of radium the less likely is permanent castration to follow and therefore recommend the administration of about 2,000 mg. hours of intrauterine radium or radon irradiation to effect control of the bleeding. Although ovarian function can be inhibited in some instances by much smaller dosages, it is well to use an adequate amount of irradiation for each patient since the tolerance of individual ovaries cannot be measured. Because the desired effect from the use of radium is primarily inhibition of ovarian function rather than a local action on the endometrium the penetrating gamma rays must be utilized fully. The local destruction produced by the soft beta rays may be prevented by the use of a capsule with a filtration capacity equivalent to that of 2 mm. of brass. A thin layer of rubber or some other organic material around the capsule will filter out the secondary soft radiation from the capsule; the resultant radiation should be almost entirely from the gamma rays and the local tissue destruction will be reduced to a minimum.

Because of the necessity for delivering the radiation to the endometrium and the ovaries the radium should be applied to the cavity of the uterus and not in the cervical canal. This method results in a maximum radiation of the desired structures without danger of destruction of the cervix. Obviously the duration of the application depends upon the

amount of radium used. but in most instances no more than 100 mg. of radium or radon should be inserted for castration.

Brown and his co-authors also describe the technique for the administration of external irradiation and present dosage tables calculated to deliver 625 roentgen, a castration dose, to the ovaries in various sized individuals.

Either procedure must be preceded by evaluation of the patient, thorough pelvic examination and curettage to rule out malignancy. If at the time of pelvic examination under anesthesia a condition which contraindicates radiation is discovered the plan of treatment should be altered.

Effectiveness

Obviously removal of the uterus will stop the bleeding in all instances. This may also be accomplished by the administration of sufficient amounts of radiation properly to selected patients; failures can for the most part be explained. The cessation of bleeding following re-radiation in patients to whom inadequate initial dosages were given must be classified as successful. The failure of the bleeding to respond in improperly chosen cases or with too little treatment cannot be classified as a failure of the method. Many patients may have one or two periods of bleeding following irradiation; consequently evaluation of results cannot be made immediately. With the exception of a small number of unexplained failures a continuation of bleeding after irradiation usually is an indication of the improper selection of cases or of an amount of therapy too small to affect ovarian function.

Morbidity and Mortality

The mortality and morbidity following the irradiation of a well-selected group of cases should be much lower than that following surgery in a comparable group. The average morbidity in collected cases is only 0.3 per cent for the irradiated group. In most instances the morbidity following irradiation is represented by an unexplained temperature elevation which may be due to a mild exacerbation of a chronic pelvic inflammatory process or to local tissue destruction. Occasionally, following the insertion of radium, a quiescent inflammatory lesion may develop into a serious acute infection with abscess formation and peritonitis.

The inevitable mortality from hysterectomy should be reduced to a minimum in operations for benign menopausal bleeding. The mortality rate of 2.5 per cent for 16,165 collected subtotal hysterectomies reported by Cashman and Frank, however, does not approach that of 0.05 per cent following irradiation in 8,175 cases. Many authors are of the opinion that the mortality rate is even higher when complete hysterectomy is performed. This obviously is a point in favor of irradiation. Danforth, on the other hand, has reported a series of hysterectomies with a total mortality rate of only 0.5 per cent. In this group the mortality rate for total hysterectomy was 0.66 per cent, for subtotal 0.8 per cent, and for vaginal hysterectomy 0 per cent.

Carcinoma Following Treatment

The incidence of uterine carcinoma developing following irradiation is 0.5 per cent in 6,883 cases collected from the literature. Since it is sometimes impossible to detect early corpus carcinoma even by careful curettage and since a few of these cases developed within a relatively short period of time after therapy, it is not unreasonable to assume that some of the malignancies were present when the treatment was instituted

and thus cannot be considered as a result either of irradiation or of leaving the uterus.

Removal of the uterus and the cervix in every patient would, of course, completely eliminate the development of uterine carcinoma, but subtotal hysterectomy does not since the incidence of carcinoma developing in the cervical stump is about 0.6 per cent or the same as that following irradiation. This incidence of stump carcinoma, however, may also be high since many of the cases reported were diagnosed within a few months of the time of hysterectomy and may have been overlooked during the original operation. Martzloff suggests that any cervical malignancy developing within three years of the hysterectomy may have been present and undiagnosed. Even though the mortality rate for total hysterectomy was the same as for subtotal it is doubtful that it would be less than the combined mortality from irradiation and carcinoma developing in the irradiated uterus.

The Present Status of the Treatment of Benign Menopausal Bleeding

In an effort to obtain information concerning the present status of the treatment of benign menopausal bleeding, a questionnaire was sent to a representative group of gynecologists throughout the United States. A tabulation of the data (Table I) reveals that 79 per cent of those contacted favor irradiation castration for the treatment of menopausal bleeding from the normal size uterus; of this group 73 per cent preferred to use radium, 18 per cent x-ray, and 9 per cent either radium or external irradiation. Of the 21 per cent who performed hysterectomy as a method of controlling the bleeding, 33 per cent favored total hysterectomy, none subtotal hysterectomy, and 67 per cent either total or subtotal hysterectomy, depending upon parity or the condition of the cervix.

TABLE I. METHODS OF TREATMENT OF BLEEDING IN THE MENOPAUSAL PERIOD ASSOCIATED WITH SMALL MYOMAS AND FROM THE NORMAL SIZE UTERUS BY A GROUP OF AMERICAN GYNECOLOGISTS

Small myomas	IRRADIATION		SURGERY	
	57%		43%	
	Radium	62.5%	Total hysterectomy	33%
	X-ray	25.0%	Subtotal hysterectomy	17%
	Either	12.5%	Either	50%
Normal uterus	79%		21%	
	Radium	73%	Total hysterectomy	33%
	X-ray	18%	Subtotal hysterectomy	0%
	Either	9%	Either	67%

For the treatment of small myomas in menopausal patients in whom the only symptom is bleeding, 57 per cent of the group utilize irradiation (62.5 per cent radium, 25 per cent x-ray, and 12.5 per cent either). Surgical removal of the uterus was considered to be the treatment of choice by 43 per cent (17 per cent subtotal hysterectomy, 33 per cent total hysterectomy, and 50 per cent either total or subtotal).

Only 27 per cent of those responding were impressed by either the complications or the mortality associated with irradiation castration. Cervical stenosis followed by retention of secretions within the uterus was mentioned by several as a complication more apt to follow radium insertion than x-ray therapy.

The majority (93 per cent) were of the opinion that the small incidence of carcinoma developing in the irradiated uterus was not sufficient indication for routine hysterectomy.

Summary

While the opinions concerning the best method for treating benign uterine bleeding in a selected group of menopausal patients are divided, the data presented here indicate that irradiation, either by x-ray or radium has certain advantages over surgery.

Even in a group of patients who are good surgical risks for the relatively simple operation of removing a normal sized uterus there will be operative deaths as well as postoperative complications. If irradiation can accomplish the same effect with a much lower morbidity and mortality rate, it might well be utilized more frequently. To achieve the best results from irradiation each case should be considered in the light of indications and contraindications before treatment is instituted and a plan of therapy, designed to produce permanent castration, should be drawn up in advance for each individual. Adequate treatment combined with a careful selection of cases should produce results favorably comparable to those with hysterectomy.

The morbidity associated with the use of either radium or x-ray may be kept at a minimum. A careful evaluation of the history, a thorough pelvic examination and dilatation and curettage to rule out malignancy should precede either x-ray therapy or the insertion of radium. The haphazard use of radium by inexperienced operators may be followed by continuation of the bleeding, complications such as local or generalized sepsis, chronic discharge from radium destruction, cervical stricture, or death of the patient.

The incidence of carcinoma developing in the uterus after irradiation is about 0.6 per cent or the same as that of carcinoma developing in the cervix after subtotal hysterectomy. The number in both groups is even lower when correction is made for those malignancies present when treatment was instituted. Since the deaths from carcinoma developing in the uterus added to the primary mortality associated with x-ray or radium castration must be fewer than the deaths following hysterectomy, it is doubtful that the potential development of carcinoma can be considered as a contraindication to irradiation.

Conclusions

1. Irradiation is a safe effective method of treating benign menopausal bleeding with a mortality rate much lower than for operation.
2. The failures are for the most part due either to poor selection of patients or to inadequate treatment.
3. The only method of eliminating uterine carcinoma is by total extirpation of the pelvic organs. The mortality from this procedure undoubtedly would exceed the combined mortality from irradiation and carcinoma following irradiation.

The author wishes to express his appreciation for the response to the questionnaires from which part of the information used in this paper was compiled.

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Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

A MATERNAL WELFARE PROGRAM FOR NEW ORLEANS

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IN JULY, 1941, there existed no definite maternal and child health program for the City of New Orleans though there were many scattered facilities which often overlapped and neglected some very vital parts of maternity and child care.

After a period of reorganization, in which the aid of the Charity Hospital (through its Director, Dr. O. P. Daly and its Assistant Clinical Director, Dr. O. Prejean) and the departments of obstetrics and pediatrics Louisiana State University Medical Center and Tulane University was secured, there is now a complete program functioning efficiently. It is this program with some interesting statistics on several new features which is here described.

Antenatal and postnatal care is furnished by Charity Hospital for patients in its vicinity who are to be delivered in that institution. In Algiers and in the St. Bernard Colored Housing Project, both of which are distant from the hospital, clinics for white and colored women are maintained in the former and for colored in the latter. These distant outpatient clinics have relieved some of the excess load of the Charity Hospital clinics and there has been a 60 per cent increase in attendance because of their proximity to the attending patients. In all housing projects of the City there are now established health stations which later will have included antenatal and postnatal clinics as soon as proper medical help may be secured. Patients in these clinics receive their delivery service at Charity Hospital because of the close cooperation between this institution and the Maternal and Child Health Division of the City Health Department.

Two other antenatal and postnatal clinics are maintained for the Louisiana State University Medical Center and Tulane University. These are for colored patients and are located on the south and north sides of the city respectively. In these clinics multiparas under para v and without any complications, are enrolled to serve as home delivery cases for teaching purposes. These cases are delivered in the home by the senior student under the supervision of the respective schools' hospital resident with the assistance of a trained maternity nurse of the Maternal and Child Health Division of the City Health Department. Approximately 60 cases per month are cared for on this service and are used strictly for teaching students the conduct of normal deliveries in the home. All abnormal cases which develop are taken to Charity Hospital. All other home delivery services have been discontinued with the exception of a low cost white service under the supervision of the Child Welfare and Child Health Associations. There are ample hospital facilities maintained by Charity Hospital which obviates the need for home deliveries other than for teaching purposes.

In order to prevent crowding of the hospital services after delivery, it was decided to institute a policy of early discharge of patients who had normal deliveries and provide them with a follow-up home nursing service which had medical advice from the resident staff of Charity Hospital. Much is now being said about

the early discharge of patients after delivery because of war conditions. In the past twelve months, 2926 patients have been sent home between the second and fifth post-partal days and of these only 30 developed complications requiring extra medical care other than nursing care given by the nursing service of Maternal and Child Health Division, which averaged three visits per case. Of these 30, only three were readmitted to the hospital, one for sapremia and two for pyelitis. The remaining 27 exhibited breast complications which were cared for in the home by the nursing staff under the direction of the resident staff. We would like to offer this as evidence that hospital deliveries with early discharge and adequate home follow-up are safer and more economical than home delivery per se. We can visualize this plan being adopted as the solution to present crowded conditions and to the scattered rural populations.

Maternal syphilis has long been present as high as 10 per cent in the colored and in from 2 to 3 per cent in the white patients in New Orleans. At our request, the above previously mentioned authorities of Charity Hospital established obstetrical-maternal syphilis clinics (three for colored, two for white). These clinics use the combined knowledge of the obstetrician and syphilologist to insure the utmost care for these patients. A thorough follow-up and family contact service is provided by the Maternal and Child Health nursing service. After pregnancy has ended, each mother is followed and therapy continued to completely eradicate the infection.

There are approximately 225 cases enrolled in these clinics at the present time and in the past twelve months 370 cases have been treated. With such a program congenital syphilis will be eradicated and eventually the more ideal state of eradication of maternal syphilis will result.

Conclusion

The maternity program of the New Orleans City Health Department has been organized and is now serving the following purposes:

1. To lower maternal and infant mortality and morbidity by giving care, instruction and supervision throughout the maternity cycle to expectant mothers who are unable to pay for a private physician.
2. To relieve congestion in the Charity Hospital maternity clinics and obstetrical wards.
3. To furnish training for physicians, medical students, and nurses.
4. To furnish postnatal care for infants and initiate and stimulate interest in pediatric follow-up examinations.
5. To provide antenatal and postnatal medical and nursing supervision for all expectant mothers who have syphilis or have had syphilis previously. Also, to provide nursing supervision of all family contacts of these mothers.

Acknowledgment is made of the aid of the Committee on Maternal Welfare of the New Orleans Medical Society, and especially to its Chairman, Dr. E. L. Zander.

Department of Statistics

A SURVEY OF CESAREAN SECTIONS IN PHILADELPHIA

Comparison Between Years 1931 and 1941*

CLIFFORD B. LULL, M.D., PHILADELPHIA, PA.

IN 1931 the Council of the Philadelphia Obstetrical Society requested me to make a study of the incidence and mortality of all cesarean sections performed in the city of Philadelphia during that year. The present is a comparative study

TABLE I. INCIDENCE OF CESAREANS AND DEATHS

HOSPITAL	NO. DELIVERIES	NO. SECTIONS	% INCIDENCE	SECTION DEATHS	% DEATHS
1	546	8	1.46	0	0.0
2	733	27	3.68	3	11.1
3	922	80	8.67	0	0.0
4	1001	37	3.69	1	2.7
5	1251	26	2.07	0	0.0
6	215	4	1.86	0	0.0
7	497	14	2.81	1	7.14
8	789	12	1.52	0	0.0
9	1077	26	2.41	1	3.84
10	544	13	2.38	1	7.69
11	818	6	0.73	0	0.0
12	52	17	32.69	0	0.0
13	379	10	2.63	0	0.0
14	673	23	3.41	0	0.0
15	1519	29	1.90	2	6.89
16	2179	122	5.59	1	0.81
17	433	28	6.46	0	0.0
18	172	7	4.06	0	0.0
19	565	8	1.41	1	12.5
20	30	0	0.0	0	0.0
21	547	16	2.92	0	0.0
22	1046	30	2.86	0	0.0
23	1075	25	2.32	0	0.0
24	114	0	0.0	0	0.0
25	728	35	4.80	1	2.85
26	365	13	3.56	0	0.0
27	391	4	1.02	0	0.0
28	505	8	1.58	1	12.5
29	920	10	1.08	0	0.0
30	1376	35	2.54	0	0.0
31	1472	44	2.98	4	9.09
32	1794	80	4.45	2	2.5
33	4	2	50.0	0	0.0
34	1392	8	0.57	0	0.0
35	1169	19	1.62	0	0.0
36	1504	18	1.19	1	5.55
37	136	3	2.20	0	0.0
38	493	20	4.05	1	5.0
39	38	0	0.0	0	0.0
40	277	1	0.36	0	0.0
41	255	9	3.52	1	11.1
42	481	11	2.28	0	0.0
43	141	0	0.0	0	0.0
44	254	5	1.96	0	0.0
45	67	1	1.49	0	0.0
(1941)	30939	894	2.88	22	2.46
(1931)	23511	573	2.43	39	6.80

*Presented at a meeting of the Obstetrical Society of Philadelphia, March 4, 1943.

for the year 1941. There is always some question as to what information may be obtained from these statistical surveys, but I believe that this comparative study will elicit several interesting points. Again we have been able to obtain the whole-hearted cooperation of the hospitals in answering the questionnaire, as well as the assistance of the Division of Vital Statistics of the Department of Public Health and the Maternal Welfare Committee of the County Medical Society. Without their cooperation this presentation would not have been possible.

Table I lists by number the 45 hospitals in Philadelphia practicing obstetrics, the total number of deliveries, the number and incidence of cesarean sections, the number of deaths and the mortality per cent. In this table it will be noted that there was a marked reduction in the mortality rate in 1941 although there was an increase in the incidence of cesarean sections.

Table II shows a comparison between the total number of births and the birth rates in 1931 and 1941, the deliveries occurring in hospitals and the number and percentage incidence of cesarean section. In this table it will be noted that the percentage of hospital deliveries increased from 66.6 in 1931 to 88.4 in 1941 and the incidence of cesarean section increased from 1.6 to 2.5 per cent.

TABLE II. TOTAL INCIDENCE OF CESAREAN SECTION

	1931	1941
Total births in city (live and still)	35,284	34,989
Birth rate per 1,000 population	17.3	17.6
Total births in hospitals	23,511	30,939
Percentage of hospital deliveries	66.6	88.4
Total cesarean sections done	573	894
Per cent of total deliveries	1.6	2.5
Per cent of hospital deliveries	2.4	2.8

Table III shows the parity of patients delivered by the abdominal method in the two surveys.

TABLE III. CESAREANS AND PARITY

	1931	1941
Total cesarean sections	573	894
Primigravidas	284	452
Multigravidas	289	442

Table IV shows the number of patients operated upon before and after the onset of labor, the number that had ruptured membranes, vaginal examinations or attempted vaginal deliveries. In all probability, those patients operated upon when in labor had not progressed further than the very early first stage although the tendency seems to be to give more women a test of labor than heretofore. In 1931 there were five patients upon whom one or more attempts at vaginal delivery were made prior to cesarean section and three of them died. In 1941, only three patients fell into this group and none of them died.

TABLE IV. CESAREANS IN RELATION TO LABOR

	1931		1941	
	No.	%	No.	%
Number of cesarean sections	573	100.0	894	100.0
Patients in labor	268	46.8	309	34.6
Patients not in labor	305	53.2	585	65.4
Membranes ruptured	108	18.8	136	15.2
Vaginal examinations	156	27.2	137	15.3
Attempted vaginal delivery	5	0.87	3	0.33

Table V shows the indications for operation. As in the previous survey, the term cephalopelvic disproportion includes all the cases of absolute contraction of the pelvis as well as the borderline cases where the fetal head was too large to enter the pelvic inlet. The increased incidence of cesarean section in cases of placenta previa and premature separation of the placenta would lead one to believe that the more radical method of treating these conditions has gained favor in the last 10 years in spite of the fact that there is still quite a controversy as to its advisability. One is impressed with the fact that previous cesarean section as the only indication, increased from 16 to 54. This would also indicate that the dictum "once a cesarean always a cesarean" has gained more followers during the last decade. Another interesting figure is the marked decrease in the number of cases delivered by cesarean section where the only indication was sterilization. This, we believe, might be attributed to the fact that puerperal sterilization done under local anesthesia is more frequently performed than cesarean section with sterilization. As usual, many of the other indications might be questioned. However, it is not the purpose of this paper to criticize but rather to make a plea for standardization of the indications for cesarean operation.

TABLE V. INDICATIONS FOR CESAREAN

	1931	1941
Cephalopelvic disproportion	339	450
Placenta previa	42	79
Toxemia and eclampsia	44	56
Premature separation of placenta	19	55
Previous cesarean as only indication	16	54
Uterine inertia	11	47
Cardiac condition	21	31
Fibroids	0	26
Abnormal presentation	26	20
Tuberculosis	5	7
Recent plastic	5	7
Habitual intrauterine fetal death	0	7
Diabetes Mellitus	0	5
Pelvic tumors	9	4
Elderly primiparas	0	4
Adhesions of old scar	2	4
Kidney disease	0	4
Ruptured uterus	3	3
Elective for sterilization	10	2
Multiple pregnancy	1	2
Appendectomy and appendicitis	0	2
Deformity of hip	2	0
Monstrosity	3	0
Ventral fixation of uterus	3	0
Miscellaneous	12	17
Unknown indication	0	8
Total	573	894

Table VI shows the type of operation performed. In comparison with 1931 when 79.9 per cent cesareans were of the high type, only 61.5 per cent were high cesareans in 1941. There was also a contrast in the proportion of low cesareans done in the two surveys. Obstetricians seem to be accepting the low cesarean operation more generally, particularly in those patients whose membranes have ruptured or who have had vaginal examinations. There were only two extraperitoneal or Waters' modification of the Latsko operation performed. This may be due to the fact that this operation supposedly is more difficult to perform. On the other hand, from my own experience in a rather large obstetric service, I believe it may be due to the fact that fewer patients were permitted to go on indefinitely in labor

and very few had attempts at vaginal delivery before coming to the operating room.

TABLE VI. TYPES OF CESAREAN OPERATION

	1931		1941	
	NO.	%	NO.	%
High	458	79.93	550	61.52
Low	103	17.97	324	36.24
Porro's	10	1.74	17	1.9
Vaginal hysterotomy	1	0.17	0	0.0
Abdominal pregnancy	1	0.17	0	0.0
Extraperitoneal	0	0.0	2	0.22
Not known	0	0.0	1	0.11
Totals	573	100.0	894	100.0

Table VII shows sterilization heading the list of incidental operations. The incidence of hysterectomy instead of myomectomy would lead one to believe that it is the operation of choice where fibromyomata of any size are present in the uterine corpus.

TABLE VII. INCIDENTAL OPERATIONS

	1931	1941
Sterilization	85	212
Hysterectomy	0	25
Salpingo-oophorectomy	5	3
Myomectomy	17	3
Appendectomy	4	1
Lysis of adhesions	0	1
Herniorrhaphy	2	1
Removal of cysts	0	6
Totals	113	252

Table VIII shows the type of anesthesia used. In 1941 inhalation types of anesthesia which included the various gases and ether, were still used more frequently, but it is encouraging to see that there is an increase in the number of cesarean deliveries under local and spinal anesthesia. With the advent of continuous caudal anesthesia, we may in the future expect a very definite decrease in the number of cesareans done under general anesthesia. For a number of years spinal anesthesia was severely condemned in all institutions throughout the city of Philadelphia. However, since the development of fractional spinal anesthesia, there has been a steady increase in its use. During the past year all of the cesarean sections which I personally performed were done under either fractional spinal or continuous caudal anesthesia and the results have been most gratifying.

TABLE VIII. ANESTHESIA USED

TYPE	1931		1941	
	NO.	%	NO.	%
Inhalation	513	89.52	762	85.23
Local	46	8.02	102	11.4
Spinal	14	2.44	28	3.13
Not known	0	0.0	1	0.11
None	0	0.0	1	0.11
Totals	573	100.0	894	100.0

Table IX shows the incidence of live births and stillbirths. It is very encouraging to note the marked decrease in the percentage of still births.

TABLE IX. INCIDENCE OF LIVE AND STILLBIRTHS

	1931		1941	
	NO.	%	NO.	%
Live births	502		874	
Stillbirths	74	12.8	30	3.3
Total births	576		904	

Table X shows the number of cases having had previous cesarean operations. In 1931, 10.2 per cent of the patients with previous cesarean had that as the only indication for the operation, while in 1941 this percentage increased to 21. Practically none of these patients had long labor previous to operation, as shown by the fact that 79 out of 107 were operated upon at the time of election in 1931, and 193 out of 256 in 1941. There was one death in this group in each series.

TABLE X. PREVIOUS SECTIONS

	1931		1941	
	NO.	%	NO.	%
No. having had previous sections	107	100.0	256	100.0
Previous section only indication	11	10.2	54	21.0
Operated at time of election	79	73.8	193	75.4
Operated while in labor	28	26.2	63	24.6
Deaths in this group	1	0.93	1	0.39

Table XI shows the very gratifying decrease in the number of maternal deaths following cesarean section in 1941 as compared with 1931.

TABLE XI. CESAREAN MORTALITY IN ALL HOSPITALS

	1931	1941
No. of cesareans done in all hospitals	573	894
No. of deaths following cesareans	39	22
Percentage of cesarean deaths	6.80	2.46

Table XII shows that although sepsis continues to hold first place as the leading cause of death among the women delivered by cesarean section, it was 9.7 per cent lower in 1941 than in 1931. It is also interesting to note the decrease in the number of deaths listed as hemorrhage and shock. This, in all probability, was due to the prompt and effective use of either plasma or blood which is made possible by the recently established Blood Banks. Attention is also called to the fact that there were no deaths from spinal anesthesia in 1941 in spite of its increased use.

TABLE XII. LEADING CAUSES OF DEATHS FOLLOWING CESAREANS

	1931		1941	
	NO.	%	NO.	%
Sepsis	18	46.15	8	36.36
Hemorrhage and shock	11	28.20	3	13.63
Cardiac conditions	2	5.12	2	9.09
Spinal anesthesia	2	5.12	0	0.0
Nephritic toxemia	1	2.56	1	4.54
Embolism	1	2.56	1	4.54
Others	4	10.25	7	31.81
Totals	39	100.0	22	100.0

Table XIII shows mortality in the various types of cesarean section.

TABLE XIII. MORTALITY IN VARIOUS TYPES OF CESAREAN SECTION

	1931			1941		
	TOTAL DEATHS			TOTAL DEATHS		
	NO.	%		NO.	%	
High	458	31	6.76	550	18	3.27
Low	103	4	3.88	324	4	1.23
Porro	10	4	40.0	17	0	0.0
Extraperitoneal	0	0	0.0	2	0	0.0
Not known	2	0	0.0	1	0	0.0
Totals	573	39	6.8	894	22	2.46

Table XIV shows the indications for cesarean in the fatal cases. This shows a general improvement in all groups.

TABLE XIV. INDICATIONS FOR CESAREAN IN FATAL CASES

	1931			1941		
	TOTAL DEATHS			TOTAL DEATHS		
	NO.	%		NO.	%	
Cephalopelvic disproportion	328	17	5.18	450	10	2.22
Placenta previa	42	3	7.14	79	3	3.79
Toxemia and eclampsia	43	8	18.60	56	4	7.14
Premature separation of placenta	19	3	15.78	55	2	3.63
Uterine inertia	7	1	14.28	47	1	2.12
Cardiac condition	21	2	9.52	31	1	3.22
Tuberculosis	0	0	0.0	7	1	14.28
Brow presentation	6	2	33.33	0	0	0.0
Ruptured uterus	3	2	66.66	0	0	0.0
Cerebrospinal meningitis	1	1	100.0	0	0	0.0
Totals	470	39		725	22	

Summary

A ten year period comparative statistical survey of cesarean sections performed in 45 hospitals throughout the city of Philadelphia is herewith presented. During this period numerous authorities have made a plea for reduction in the incidence of cesarean section, but their efforts have been of no avail as far as the city of Philadelphia is concerned.

The decrease in maternal mortality in spite of the increased number of cesarean sections performed, proves that better judgment has been used in the selection of cases for hospitalization, the time element, the type of operation performed, and the anesthesia used. Errors in judgment where these factors were concerned were probably the most frequent causes of fatalities.

The decrease in maternal and fetal mortality would indicate that cesarean section is now performed when it is truly the procedure of choice and is not used as frequently as a last resort when trial labors and attempted vaginal deliveries have failed.

It has been the consensus of opinion that a statistical survey is of little value, but a comparative statistical survey would seem to be of greater aid in determining whether progress has been made during a definite period of time.

In conclusion, it is recommended that a committee be appointed to make suggestions as to standardization of the various indications for the operation of cesarean section so that in future surveys these indications would be more accurate and less confusing.

Appreciation is expressed to Dr. Ruth Hartley Weaver, Assistant Director of Health of the City of Philadelphia, and Miss Dorothy Malkiel, Secretary of the Maternal Welfare Committee of the County Medical Society, for their assistance in the compilation of these statistics.

Reference

Lull, Clifford B.: *Caesarean Section in Philadelphia (A Survey of 1931)*. Published by the Council of the Philadelphia Obstetrical Society.

807 SPRUCE STREET

Discussion

DR. J. MARCH ALESBURY.—I agree with Dr. Lull that the death rate from cesarean section has decreased. Part of this reduction is due to the use of low cervical section rather than the high in cases contaminated. We must remember that in 1931 we had a total of 269 maternal deaths, of which only 39 deaths followed cesarean section. Accordingly, 14 per cent of the 269 deaths in 1931 were due to cesarean section. In 1941, we had a total of 90 maternal deaths but still had 22 deaths following cesarean, or approximately 24 per cent of the maternal deaths.

In 1941, of the 22 deaths following cesarean, 14 were allocated by the Committee on Maternal Welfare as being P-1 deaths. That means that 63 per cent of the cesarean deaths in 1941 were due to error in judgment, technique, et cetera. When we find that we have an increase in the percentage of maternal deaths from 14 per cent due to cesarean section to 24 per cent, I think we have plenty of room for improvement.

DR. EDWARD SCHUMANN.—I would like to take issue with Dr. Alesbury about the increased percentage of deaths due to cesarean section. The relatively greater number of deaths in cases treated by cesarean section is due to the greater improvement in general obstetrics resulting in an improvement in the maternal death rate as a whole. Unless statistics are broken down you cannot arrive at a sensible conclusion.

If we made a survey of the morbidity and mortality of any surgical operation from 1931 to 1941, you would have comparable improvement in all types of surgery. I expect that if Dr. Lull makes a survey in 1951, he will find a still lower *number* of deaths, but a still higher *percentage* of deaths from cesarean section.

DR. THADDEUS MONTGOMERY.—I would like to ask if the statistics include operative procedures done for rupture of the uterus. I know of two cases of death following such operations and would like to raise the point if it is proper to include the operation "laparotomy" under the head of cesarean section?

The other point to be raised is the question of the extraperitoneal section. A few years ago an enthusiast asked why we had not been doing it and thought we were behind the times, but even at that time, it seemed to me there were very few occasions which called for this operation. If one is to perfect himself in this operation, which is undoubtedly more difficult technically, he has to operate on many patients with the indications practically nonexistent. I doubt that we have the opportunity in the city for one individual to perfect himself in this operation.

DR. NORRIS W. VAUX.—I believe the improvement in mortality is partially due to the fact that the Maternal Welfare Committee in its discussion throughout the City of Philadelphia calls for consultation of obstetricians of reputation after 24 hours of labor without progress, to decide whether or not cesarean section should be performed. I have no reason to suppose that in 1931 these sections were done promiscuously or without consultation, but I am convinced there is something in the improvement of our statistics which the Maternal Mortality Committee has taken cognizance of in urging the hospitals to live up to this consultation program. As has been mentioned, the incidence of deaths is probably higher in the section cases but, after all, the patient is getting better professional treatment, which in the end will show an improvement in maternal death rate from cesarean section. We are improving regardless of whether statistics lie or tell the truth and in 1951 I hope we will see steady improvement and lasting results.

DR. PHILIP F. WILLIAMS.—The Committee on Maternal Welfare used the frequency of types of operation in the first survey in their analysis of cesarean deaths for the first three years' work of the Committee. The present survey shows many points for discussion. One of them is the marked increase in the low cervical section, an advance which has been made very slowly in this city. It is interesting to recall in this connection that Falls of Chicago showed there was not much difference in the mortality between the classical and the low section in a large series of cases. Last year, Schumann's paper made it quite evident that there was not much need for the extraperitoneal type of cesarean section, for at least, one year, 1941, in Philadelphia. For in that year there were very few infected obstructed labors admitted to the hospitals of Philadelphia.

It was interesting to note that one out of four women who had a cesarean section reported in this second survey was sterilized. In twenty-five of these sterilizations the uterus was removed and Dr. Lull has stated that all of these hysterectomies were done because of fibroids. If this is the case, I think we are missing some points to remove the uterus when a hysterotomy has been done in some cases of nephritis or cardiac deaths where we want to sterilize the patient. Stander has made this point clear in his discussion of the treatment of pregnancy and complicating chronic nephritis. I think that if such a high percentage, practically 25 per cent had to be sterilized at the time of cesarean, that the breakdown of the indications of sterilizing them would be of considerable interest.

Finally, I feel that in spite of transfusions and the use of sulfanilamide and the increased use of the low section, that a certain proportion of the reduction in the mortality from cesarean sections shown by comparing the two surveys must be attributed to the open discussions of mortalities in the meetings of our County Medical Society Committee on Maternal Welfare.

DR. LULL (closing).—In going over these records I was distinctly impressed with the improvement which has been shown in the practice of obstetrics during the past decade. Particularly is this improvement evident in those cases upon whom vaginal examinations were performed and whose membranes had ruptured previous to the operation of classical cesarean section. A great deal of credit should be given to the Maternal Mortality Committee for their efforts in bringing about these improvements.

Dr. Montgomery has brought up the question of the Waters' operation. I agree with him that we do not see the badly infected or mishandled case as frequently as we used to and, therefore, the operation is not performed as frequently as in some reported series.

Finally, it has been a great pleasure to see how the question of the type of operation and the anesthetic used, together with adequate fluid balance, blood transfusion, careful preoperative preparation and every sensible postoperative care, have all played an important part in saving the life of a good many patients.

Department of Reviews and Abstracts

Selected Abstracts

Extrauterine Pregnancy

Leech, R. B.: A Case of Combined Intra-Uterine and Extra-Uterine Pregnancy, Brit. M. J. 2: 805, 1941.

The author reports a case in a Uganda native.

The patient had cyclic bleeding during the first six months of her pregnancy. Two weeks from term, abdominal examination revealed the uterus to be enlarged to a size compatible with menstrual history, but flanked by two masses resembling fetal heads in size. A provisional diagnosis of fibroids was made.

The patient was delivered at term, by the local midwife, following a normal labor, of a five and one-half pound living infant. Two days later, the patient began to complain of abdominal pain, which persisted for three weeks. She then sought aid at the central hospital, where she was delivered by laparotomy of a living six-pound infant which was lying free in the peritoneal cavity. The amniotic sac had ruptured spontaneously, presumably at the time of the onset of symptoms two days following delivery of the intrauterine fetus. The placenta was attached in the region of the right ovary.

Three hundred and six cases of combined pregnancy have been collected by Mitra, of which about 3 per cent resulted in the delivery of both infants alive.

FRED L. ADAIR AND RAYMOND L. YOUNG.

Kulenkampff, D.: Diagnosis of Abdominal Bleeding in Extrauterine Pregnancy, Zentralbl. f. Gynäk. 65: 379, 1941.

The author discusses the many possibilities of error in attempting to secure abdominal fluid by puncture in suspected hemorrhage of ectopic pregnancy. His criterion for determining that any blood found in the sample drawn by puncture is truly free blood is: rouleaux formation is never seen, but countless erythrocytes have assumed a thorn apple (crenated) shape.

R. J. WEISSMAN.

Ramos, A. P., and Collazo, A. G.: Value of Quantitative Determination of Chorionic Gonadotropin in the Diagnosis of Ectopic Pregnancy, Rev. méd. brasil. 10: 111, 1941.

From the premise that the production of chorionic gonadotropin is in direct relation to the area affected by placental trophoblastic activity, as evidenced by its quantity in multiple pregnancy, the authors felt that deficiency of implantation areas, which often occur in ectopic pregnancy, would give a relatively low value for chorionic gonadotropin concentration in blood serum. In cases in which there is deficient or subnormal villous implantation in utero, in the first few months of pregnancy values between 1,000 and 1,500 units per liter of blood serum are found. When these values fall below 1,000 units, fetal death is indicated if the content steadily decreases, of very early pregnancy if the values are increasing in serial

tests, soon rising above 1,000 units. In some cases, however, the values are maintained in the neighborhood of 750 units, and when this is added to strongly suggestive physical findings, the diagnosis of ectopic pregnancy is almost certain. Still lower values, yet over a minimum of 150 units suggest ectopic pregnancy with fetal death. Except for tubal abortion of some days' duration, with organization of the hematocele, ectopic pregnancy may be ruled out if chorionic gonadotropin values fall below 150. Over 20 cases are cited in support of the author's work.

R. J. WEISSMAN.

Bretz, M.: Mistaken Diagnosis of Extrauterine Pregnancy due to Prior Perforation of Uterus, *Zentralbl. f. Gynäk.* 65: 498, 1941.

A 30-year-old woman whose chief complaint was right lower quadrant pain had aborted six years previously at two months' pregnancy; five years previously she had a normal full-term delivery with onset of severe bleeding seven weeks later. The family physician performed a dilatation and curettage. Since then the patient's menses had been irregular, giving a picture typical of ectopic pregnancy. At laparotomy an enlarged gravid uterus was found. Deeply embedded in the anterior uterine wall was an adhesion as thick as a pencil which passed from the insertion in the uterus to the left between the left tube and ovary, behind the suspensory ligament, crossing the left tube at the uterine cornu, thus more or less strangulating the tube and ovary and passing on across the anterior aspect of the uterus and up to the right colic flexure. The author concludes that an epiploic appendage had been drawn into the uterine perforation by the curette. The affected adnexa were removed and recovery was uneventful.

R. J. WEISSMAN.

Neumann, O.: Infected Interstitial Pregnancy, *Zentralbl. f. Gynäk.* 64: 1725, 1940.

According to the author's statistics one interstitial pregnancy is found to 100 extrauterine pregnancies. The author discusses the possible fates of the ovum. A para ii, after two months of amenorrhea experienced mild bleeding of four weeks' duration. In the fourth month since the onset of amenorrhea a flow occurred associated with severe cramps. This the patient assumed was her menses. In the middle of the fifth month she was seized with severe lower abdominal pain and was subjected to laparotomy with a diagnosis of ectopic pregnancy with peritonitis. The abdomen was full of purulent exudate redolent of *B. coli*. Streptococci and staphylococci and fusiform bacilli were also found. An egg-sized tumor was found at the right uterine cornu and on its lower aspect a perforation was seen to be exuding pus. Hysterectomy with drainage was done without avail. The uterine wall was 2 cm. thick and a pigeon's egg-sized fetal sac was found in the tumor, with 2 mm. of muscularis on either side. Microscopically diffuse leucocytic infiltration was found in the membranes. The author concludes that the death of the ovum left a necrotic locus minoris resistentiae for invasion by bacteria by haematogenous or other routes. No mention was made as to whether attempts at abortion had been made by the patient.

R. J. WEISSMAN.

Schwarz, M.: Full-Term Ectopic Pregnancy With Viable Infant, *Zentralbl. f. Gynäk.* 65: 204, 1941.

Schwarz reports a case of extrauterine pregnancy going to full term. The fetus was found enclosed in its amniotic sac and the placenta was implanted on the peritoneal surface of the uterus. There were a few adhesions to the lateral pelvic walls. The child was delivered and breathed spontaneously. The uterus was amputated. Mother and child made an uneventful recovery.

R. J. WEISSMAN.

Pignoli, Renato: Upon the Existence of a Capsular Membrane in Tubal Pregnancy, *Ginecologia* 18: Series 2, 443, 1940.

The author reports that he was able to demonstrate the presence of a capsular membrane in each of two cases of tubal pregnancy. This capsular membrane in tubal pregnancy was comparable to the decidua reflexa in intrauterine pregnancy. Two photomicrographs are included in the article.

CLAIR E. FOLSOME.

Ballantyne, E. N., Murray, K., and Fraser, R. J.: Interstitial Pregnancy After Homolateral Salpingectomy, *Canad. M. A. J.* 43: 560, 1940.

A case of interstitial pregnancy terminating in uterine rupture during the fifth month is reported. The patient had had a previous salpingo-oophorectomy on the same side for an extrauterine pregnancy and a dermoid cyst. At least 25 cases in which an interstitial pregnancy has occurred subsequent to a homolateral salpingectomy are recorded in the literature.

The diagnosis before rupture of the interstitial pregnancy is difficult but should be kept in mind.

The palpation of a mass attached to one cornu by a broad base in the presence of symptoms suggesting pregnancy is characteristic. Cornual excision is the operation of choice in cases where the pregnant sac is not too large and supravaginal hysterectomy in the more advanced cases.

CARL P. HUBER.

Reist, A.: Rare Ectopic Pregnancy in the Form of a Primary Cervical Pregnancy, *Monatschr. f. Geburtsh. u. Gynäk.* 112: 65, 1941.

The author reports a case of primary cervical pregnancy and reviews the literature. The mortality among the 44 reported cases was 25 per cent and was chiefly due to hemorrhage. The safest treatment for this rare condition is removal of the uterus as soon as the diagnosis is made. In very early cases, however, it is possible to treat the condition by removal of the pregnancy, ligation of the cervical blood vessels, tamponade, and amputation of the cervix.

J. P. GREENHILL.

Toxemia

Whitacre, Frank E., and Fang, L. Y.: Fatty Degeneration of the Liver in Pregnancy, *J. A. M. A.* 118: 1358, 1942.

A case of fatty degeneration of the liver with recovery is reported. A cesarean section was done and the woman recovered. The life of such a patient depends upon vigorous treatment with dextrose and termination of the pregnancy by the most conservative means. Blood chemistry will usually indicate extensive liver damage. The patient had less advanced stage of acute yellow atrophy than is seen usually in pregnancy. It is the belief of the authors that patients with this disease die from hypoglycemia rather than from the extent of the liver damage.

WILLIAM BERNAN.

Foley, E. J.: Toxemia of Pregnancy in the Guinea Pig, *J. Exper. Med.* 75: 539, 1942.

A fatal disease of late pregnancy and the early puerperium is reported from the guinea pig colony of the department of Bacteriology of the Notre Dame University. Of the 214 deaths from all causes occurring since July, 1940, 47 seemed to fit this category. The disease was sudden in onset, and marked by prostration

and respiratory distress. Death occurred within twenty-four hours. At autopsy the liver was swollen and bright yellow in color. Microscopically it contained a great deal of fat. There was frequent edema of the lungs and occasional pneumonia. No consistent bacterial agent could be found. The disease occurred in primiparas more often than in multiparas. Unlike the report of Greene of a somewhat similar disease in the rabbit colony of the Rockefeller Institute at Princeton, there were no cases not associated with pregnancy.

T. M. HELLMAN.

Shute, E.: The Use of Vitamin P in the Edema of Pregnancy Toxemia, *Canad. M. A. J.* 45: 542, 1941.

A preparation of citrin (vitamin P) was given to 20 edematous women in late pregnancy, with the edema ascribable to pregnancy. It was also given to a pregnant woman in late pregnancy showing cardiac edema and to a nonpregnant woman having hypertension and edema. The visible edema and weight were unaffected in all cases.

CARL P. HUBER.

Lange-Sundermann: Treatment of Hyperemesis Gravidarum With Adrenal Cortex Hormone Cortiron, *München. med. Wchenschr.* 87: 808, 1940.

Dr. Lange-Sundermann discusses briefly the physiology of the adrenal cortex in pregnancy and reviews the literature on this subject, and he feels that it has now become quite clear that hormonal hypofunction in pregnancy may be the cause of hyperemesis gravidarum, and that it is necessary in pregnancy to have a hypertrophy of the adrenal in order that the pregnant woman might remain healthy and be able to do her work.

He cites his own series of 27 patients of hyperemesis, placing them in 3 classes according to the severity of their symptoms. He administers a synthetic adrenal cortex hormone (cortiron), his dosage varying with the individual and then gives his results stating that a synthetic adrenal cortex hormone (cortiron) is a very effective, prompt and relatively cheap medication in the treatment of hyperemesis gravidarum.

C. E. PROSHEK.

Demmond, E. Carson: Conservative Treatment of Eclampsia, *J. M. A. Georgia* 30: 88, 1941.

In the opinion of the author eclampsia can almost be eliminated by careful prenatal supervision with interruption of the pregnancy before the toxemia is too advanced. Eclamptic convulsions should be controlled by morphine, magnesium sulfate intravenously, and the barbiturates before any measures for delivery are instituted. After recovery from shock, delivery should be consummated by conservative measures, labor being induced by medical means, or artificially rupturing the membrane, with assistance to the patient during the second stage of labor by means of forceps.

Accouchement forcé by manual or instrumental dilatation of the cervix, cervical incisions, or vaginal hysterotomy cannot be too strongly condemned. Cesarean section should not be invoked except in those cases with a strong obstetric indication. Careful postpartum supervision is necessary with particular attention to sedation, blood pressure, and fluid intake and output. Forty ounces of urine a day keeps the convulsions away! No future pregnancies are advisable for at least two or three years, and then only if kidney function, blood pressure, and blood chemistry findings are satisfactory.

J. P. GREENHILL.

Beruti, Josue A., Diradourian, Jorge, and Ahumada, Jorge L.: Results of Treatment for Eclampsia, *Arch. de la Clinica Obst. y Ginec.* 1: 69, 1942.

This is a statistical study of 339 cases of eclampsia treated in the Obstetrics and Gynecology Clinic "Eliseo Cantón" from 1911 to 1937, with the purpose of comparing radical and conservative methods of treatment. To avoid errors in evaluation the cases were divided into two groups according to the severity of the condition. The indications of the Comité de Londres (1922) were used as criteria. Those cases presenting two of the following five findings were considered severe: (1) coma, (2) pulse above 120, (3) temperature above 39.4 C, (4) systolic blood pressure above 200 mm. and (5) massive albuminuria.

Of the 339 cases, 13.5 per cent occurred ante partum, 64.8 per cent during labor and 21.5 per cent post partum. The total mortality was 18.8 per cent.

The 46 cases of eclampsia during pregnancy (before onset of labor) were divided into four groups according to the treatment employed: (1) active treatment, i.e., abdominal or vaginal cesarean section and all obstetrical manipulations resulting in immediate termination of labor, (2) classical treatment of Stroganoff, i.e., narcotics and sedatives combined in some cases with rupture of membranes and low forceps delivery, (3) the Stroganoff method interrupted or followed by active intervention when the patient's condition remains unimproved or becomes worse, (4) other treatments including venesection, special serums, etc. The authors claim that, despite the small number of cases in each group, the superiority of the Stroganoff method over the active method was definitely shown by the lesser mortality (corrected) in the former (18.1 per cent as compared with 40 per cent). The mortality with the active method was lower when combined with the Stroganoff treatment (22.4 per cent). Treatments other than these two were least effective (mortality 50 per cent). The active method involved a high fetal mortality (40 per cent) which the author feels is not surprising since delivery is almost always by the vaginal route and highly traumatic. With the Stroganoff treatment fetal mortality was only 14.2 per cent. The total fetal mortality in the 46 cases was 25 per cent.

The 220 intra-partum cases of eclampsia were classified according to the treatment as in eclampsias of pregnancy with the addition of a fifth group consisting of active treatment followed immediately by Stroganoff's method in the form advocated by Stoeckel. The mortality with the active method in these cases was 20.3 per cent, less than in the eclampsias of pregnancy. The author believes this is reasonable since labor is less precipitate and operations by the vaginal route are less complicated. When the Stroganoff method was combined with the active method, mortality dropped to 15 per cent. The best results (12.4 per cent mortality) were obtained with the Stroganoff method alone; the worst (47.3 per cent) when the Stroganoff method was abandoned because of the aggravated condition and obstetric intervention (high and low cesarean or "accouchement forcé") was used. The authors consider that this high mortality is in part due to the fact that the cases involved were the most serious ones, but that the change in method also played an important role. The good results in the group given miscellaneous treatments (mortality 13.7 per cent), according to the authors, demonstrates the fallacies which exist in statistics dealing with small numbers. Fetal mortality in the entire series was higher (35.1 per cent) than in the eclampsias of pregnancy and in the group which received Stroganoff treatment followed by active intervention was tremendous (70.5 per cent).

In the 73 cases of puerperal eclampsia the Stroganoff method was not remarkably better than other methods such as venesection and special serums. The authors point out, however, that there were twice as many serious cases in the Stroganoff group as in the group treated by other methods and comparing the two groups according to mortality in these serious cases, the Stroganoff treatment involved half as great a mortality (21.4 per cent as compared to 42.8 per cent).

The data were finally analyzed by dividing the 27 years included in the survey into three periods of nine years each. The total mortality was 21.1 per cent for the first period, decreased to 17.6 per cent in the second and remained at this level (17.1 per cent) in the third period. This lack of progress in the third period is due to an increase in the relative number of serious cases. Fetal mortality was appreciably decreased from 1.05 per cent in the first nine year period to 0.74 per cent in the second and finally 0.31 per cent in the third. The authors attribute this reduction to better prenatal care, better preparation of the doctors and increased education of the public.

The authors conclude that the Stroganoff treatment, in all circumstances, offers the best prospects of survival for both mother and child.

J. P. GREENHILL.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF MARCH 9, 1943

The following papers were presented:

A Twenty-Six Day Human Embryo. Wm. E. Studdiford, M.D. (For original article, see page 230.)

Premature Separation of the Normally Implanted Placenta. John A. O'Regan, M.D. (by invitation). To be published in a later issue.

PHILADELPHIA OBSTETRICAL SOCIETY

MEETING OF FEBRUARY 4, 1943

The following paper was presented:

Fetal Malposition: Prevention and Treatment With Special Reference to Breech Presentations Including Experience at the Johns Hopkins Hospital With 1,400 Cases. Nicholson J. Eastman, M.D. (by invitation).

MEETING OF MARCH 4, 1943

The following papers were presented:

An Unusual Fetal Teratoma, With Interesting Radiologic Aspects. F. F. Borzell, M.D. (by invitation), and L. E. Viteri, M.D. (by invitation).

A Survey of the Cesarean Sections Done in Philadelphia During the Year 1941. Clifford B. Lull, M.D. (For original article, see page 314.)

Clinical and Experimental Studies Suggesting the Probable Role of the Pituitary in the Causation of the Late Toxemia of Pregnancy With Hypertension. J. Q. Griffith, M.D.

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 19, 1943

The following papers were presented:

Excretion of Estrogens and Gonadotropins in Pregnancy. Fred L. Adair, M.D. and Ruth M. Watts, Ph.D. (For original paper, see page 183.)

The Treatment of Syphilis in Pregnancy by the Five-Day Massive Dose Method. Herbert Rattner, M.D. (by invitation). (For original paper, see page 255.)

MEETING OF MARCH 19, 1943

A Panel Discussion on Benign Bleeding at the Time of the Menopause. Radium, Dr. M. E. Davis. X-ray, Dr. Herbert E. Schmitz. Surgery, N. Sproat Heaney.

MEETING OF APRIL 16, 1943

The following paper was presented:

Carcinoma of the Cervix. Consideration of Certain Factors Pertaining to Its Control. Norman F. Miller, M.D., Ann Arbor, Michigan. (By invitation.)

Item

American Board of Obstetrics and Gynecology

The annual meeting of the Board was held at Pittsburgh, Pennsylvania, from May 20 to May 25, 1943, at which time one hundred and eight candidates were certified.

A number of changes in Board regulations and requirements were put into effect. Several of these changes are designed to broaden the requirements for candidates in Service. Examples are the allowance of a stipulated amount of credit toward special training requirements for men in Service and assigned to general surgical positions, special training allowances on a preceptorship basis for men assigned to obstetric or gynecologic duties in military hospitals and working under the supervision of Diplomates or recognized obstetrician-gynecologists, as well as credit toward the "time in practice" requirement of the Board to be allowed for time in military service.

The Board will no longer require a general rotating internship, but will now accept a one-year intern service, although the rotating internship is preferable. Such services must be in institutions approved by the Council on Medical Education and Hospitals of the A. M. A. Lists of such institutions are published regularly in the Educational Number of *The Journal of the A. M. A.*

The privilege of reopening applications by candidates who have been declared ineligible has been extended to two years from date of filing the application, instead of one year.

The Board has ruled temporarily to excuse men in Military Service from the submission of case records at the stipulated examination times, thereby permitting them to proceed without further delay with the Board examinations. This does not obligate the Board, however, to waive the case record requirement for such candidates. Plans have been made to provide similarly for Service men upon their eventual discharge from the Armed Forces, and to permit the greater use of operations done while in residency or in civilian practice before the War.

The next Part I examination of the Board (written paper and submission of case records) will be held on Saturday afternoon, February 12, 1944, at a place convenient to the location of the candidate, whether he be in civilian or military life. Applications must be in the Office of the Secretary by November 15, 1943, ninety days in advance of the examination date. The time and place of the Spring 1944 (Part II) examination will be announced later.

Prospective applicants or candidates in Military Service are urged to obtain from the Office of the Secretary, a copy of the "Record of Professional Assignments for Prospective Applicants for Certification by Specialty Boards" which will be supplied upon request. This record was compiled by the Advisory Board for Medical Specialties and is approved by the offices of the Surgeons-General, having been recommended to the Services in a circular letter, No. 76, from the War Department Army Service Forces, and referred to as the Medical Officers Service Record. These will enable prospective applicants and candidates to keep an accurate record of work done while in Military Service and should be submitted with the candidate's application, so that the Credentials Committee may have this information available in reviewing the application.

Applications and bulletins of detailed information regarding the Board requirements will be sent upon request to the Secretary's Office, 1015 Highland Building, Pittsburgh, Pennsylvania.

PAUL TITUS, M.D., Secretary.

Candidates certified (total 108) by American Board of Obstetrics and Gynecology at the May, 1943, meeting held at Pittsburgh, Pa.:

- | | |
|---|---|
| Angelucci, Helen M., 1209 S. Broad St., Philadelphia, Pa. | Cavins, Alexander W., 221 S. 6th St., Terre Haute, Ind. |
| Barber, Richard R., Capt., M.C., 125 Holmes Ave., Glenbrook, Conn. | Chapman, Eugene Rhea, Lt. Col., 11th Reg't. Med. Replacement Training Center, Camp Barksley, Tex. |
| Barker, John Russell, 1101 Beacon Street, Brookline, Mass. | Chrisman, Irving, 423 Broadway, Paterson, N. J. |
| Belous, Leon P., 1930 Wilshire Blvd., Los Angeles, Calif. | Christie, Frank G. S., 178 George St., Sarina, Ontario |
| Berman, William, 1st Lt., Station Hospital, Fort Riley, Kan. | Ciner, Leonard F., Lt., M.C., Post Dispensary Marine Barracks, Quantico, Va. |
| Bobrow, Morris L., 590 West End Ave., New York, N. Y. | Conway, James F., 1101 Beacon Street, Brookline, Mass. |
| Borson, Josephine, 2490 Channing Way, Berkeley, Calif. | Corbit, John D., Jr., 3815 Chestnut St., Philadelphia, Pa. |
| Bosch, Leon C., 512 Medical Arts Building, Grand Rapids, Mich. | Cromer, J. Keith, 1801 Eye Street, N. W., Washington, D. C. |
| Boyce, Allen C., Capt., Utah Quartermaster Depot, Ogden, Utah | Dailey, W. Paul, 901 N. Second St., Harrisburg, Pa. |
| Boyd, Benjamin Hartwell, 56 Fifth Street, N. E., Atlanta, Ga. | Daily, William T., 142 Joralemon Street, Brooklyn, N. Y. |
| Bradbury, William C., 1137 Second St., Santa Monica, Calif. | Day, Lois A., 102-10 2nd Ave., S. W., Rochester, Minn. |
| Brandt, Albert J., 413-17 Dollar Bank Bldg., Youngstown, Ohio | Deeds, D. Dalton, Buffalo General Hospital, Buffalo, N. Y. |
| Branscomb, Louise, Woodward Bldg., Birmingham, Ala. | Edgerton, Glenn S., Capt., Station Hospital, West Point, N. Y. |
| Briscoe, Clarence Conway, Medical Tower, 255 S. 17th St., Philadelphia, Pa. | Ellis, George J., 1150 Connecticut Ave., N. W., Washington, D. C. |
| Bristoll, Donald A., 55 West Main Street, New Britain, Conn. | Factor, Joseph Lt., M.C., U.S.N., U. S. Naval Hospital, Philadelphia, Pa. |
| Brody, Simon, 642 Eastern Parkway, Brooklyn, N. Y. | Fairo, Carroll Judson, Lt. Comdr., U. S. Coast Guard Training Station, St. Augustine, Fla. |
| Burwell, John C., Jr., Capt., Nautilus Hospital, Miami Beach, Fla. | |
| Caffee, Henry Hollis, Clay County, Oneida, Ky. | |

- Filler, William, 37-18 73rd St., Jackson Heights, N. Y.
- Forman, Isador, 2118 Pine Street, Philadelphia, Pa.
- Frank, Richard, 25 E. Washington St., Chicago, Ill.
- Frankel, Arthur N., Capt., 34th Evacuation Hospital, Camp Barkeley, Tex.
- Frankel, Jesse M., Capt., Co. B 5th Bn., M.R.T.C., Camp Pickett, Blackstone, Va.
- Galsterer, Edwin C., 128 S. Jefferson Ave., Saginaw, Mich.
- Garber, Stanley T., 2500 Melrose Ave., Cincinnati, Ohio.
- Gillett, Raymond Earl, Northern Permanente Foundation Hosp., Vancouver, Wash.
- Godinez, Marcos A., Lt., M.C., U.S.N., Amphibious Training Base, Camp Bradford, N. O. B., Norfolk, Va.
- Goodman, Leroy, Capt., 4738 Oak Street, Kansas City, Mo.
- Gordon, Harry, 975 Walton Avenue, New York, N. Y.
- Gorman, Arthur J., 122 Commonwealth Avenue, Boston, Mass.
- Gulick, James B., 144 So. Harrison St., East Orange, N. J.
- Hammerly, Fred, 1105 Equitable Bldg., Los Angeles, Calif.
- Hart, Benjamin F., 250 N. Ottawa St., Joliet, Ill.
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- Hellman, Louis M., Lt., U.S.N., Johns Hopkins Hospital, Baltimore, Md.
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- Hochman, Samuel, 325 West 86th St., New York, N. Y.
- Hopper, Edward B., 65 South Street, Stamford, Conn.
- Huggins, Victor S., 80 Glen Road, Brookline, Mass.
- Jones, Charlotte A., 303 East 18th St., New York, N. Y.
- Jordan, Frank F., Carnegie Medical Bldg., Carnegie at E. 105th St., Cleveland, Ohio.
- Kaderabek, Erwin J., 144 S. Harrison St., East Orange, N. J.
- King, Allan E., 1801 Eye Street, N. W., Washington, D. C.
- Klor, Samuel J., Capt., 4002 Winthrop Ave., Indianapolis, Ind.
- Kraff, Harry, 60 Seaman Avenue, New York, N. Y.
- Lambertus, Paul T., Quincy Clinic, Quincy, Ill.
- Lampman, Harold Heath, 571 Fisher Bldg., Detroit, Mich.
- Lounsbury, James B., 201 N. Front St., Wilmington, N. C.
- McLean, Lewis F., 826 W. Delavan Ave., Buffalo, N. Y.
- McMann, Walter S. L., Army Air Base, Savannah, Ga.
- McMurrey, Allen L., 1204 Eagle St., Houston, Tex.
- McSweeney, Daniel J., 47 Bay State Road, Boston, Mass.
- Mays, Clifford Raymond, 1753 Line Ave., Shreveport, La.
- Mazzola, Nunzio Joseph, 133 Clinton Street, Brooklyn, N. Y.
- Melone, Horatio R., 800 Diversey Parkway, Chicago, Ill.
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- Mullins, Julius H., Major, Station Hospital, Ft. McClellan, Ala.
- Murphy, Joseph P., Capt., 79th General Hosp., Camp White, Medford, Ore.
- O'Hara, Gerald P., 490 Post Street, San Francisco, Calif.
- Patterson, John K., Comdr., 429 E. Padre St., Santa Barbara, Calif.
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- Rucker, Edwin Macrae, Station Hospital, Camp Shelby, Miss.
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- Schwiegler, Raymond A., Capt., M.C., Station Hospital, Camp Barkeley, Tex.
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- Siegal, Henry A., 1st Lt., 310th Medical Battalion, APO 85, c/o Postmaster, Shreveport, La.
- Siegel, Irving, Capt., Station Hospital, Randolph Field, Tex.
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- Sill, Henry W., Henry Ford Hospital, 136 Calvert St., Detroit, Mich.
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Correspondence

Constriction Rings and Epinephrine

The question of the effect of adrenalin upon constriction rings has been recently revived. In an article in the April issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, Brown and Wilder conclude that epinephrine is not only useless in the treatment of this complication but is actually dangerous. They base their conclusions upon some hystero-graphs (the number was not stated) of the laboring and parturient uterus after the administration of $\frac{1}{2}$ to 1 minim of a 1:1,000 solution intravenously, and upon clinical observations, the nature of which is not stated. The authors take exception to laboratory observations being transferred directly to clinical practice without the necessary critical study to determine their value or safety. Then as an exhibition of their own critical powers, they group under the term "contraction rings" all those variants of uterine contraction known as Bandl's rings, retraction rings, hourglass contractions and others. Further on in the article, it is evident that they include a rigid cervix in the "others." At least they argue that epinephrine does not relax the cervix, for had it done so, the uterine contractions would have expelled the hydrostatic bag. They quote Rudolph to the effect that all are an exaggeration of the normal process of uterine contraction and retraction. From their article one would think that Rudolph made no distinction between the various kinds of rings. As a matter of fact, Rudolph coined the very descriptive term "constriction ring" for the type of ring that formed about the fetus so tightly that no further progress of the birth of the baby was possible so long as the ring persisted. Some of the constriction rings are reversible and some irreversible. Rudolph says the term, retraction ring, should be reserved for the exaggerated line of demarcation between the thickened active part of the uterus and the passive lower uterine segment that forms in an obstructed labor. This ring is not a fixed ring like the constriction ring, but ascends as the lower uterine segment becomes thinner, and unless properly treated, rupture of the uterus may result. If Rudolph's suggestion as to the use of these terms were followed, there would be less confusion.

The authors are equally misleading when they refer to my work. "In 1927 Rucker, working on the hypothesis of the relation of the sympathetic system to uterine contraction, reported a relaxation effect of epinephrine on the contraction rings in dystocia. His records are in part graphic, but for the most part are clinical interpretations." My first communication (*Southern Med. J.* 18: 412, 1925), which the authors entirely ignored, was entirely "graphic." When I began the investigation, I had no preconceived idea. I was merely trying to find out why in some of my caudal anesthesia cases, there followed cessation of uterine contractions as shown by a recording manometer attached to a Voorhees bag within the cervix, and some were followed by no such effect. When these

records were reviewed "critically," it was seen that when adrenalin was added to the procaine, there was a cessation of uterine contractions. When no adrenalin was added to the procaine solution, the uterine contractions continued unabated. The next step was very simple. The adrenalin was administered hypodermically, independently of any anesthesia and four times out of five there was a cessation of uterine contractions as shown by the kymograph. In 20 per cent of the cases, no effect whatever was observed. This was so contrary to the current opinion of the action of epinephrine that it was a comfort when Bourne and Burn obtained the same results independently in England.

The authors show 6 graphs which were evidently tracings of the originals. These add "color" to their article. They show nothing definite, but one would hardly expect to see any effect from $\frac{1}{2}$ minim of epinephrine. The steep-like contraction in their second graph could very easily have been a gasp, a sigh, or a cough. There is certainly nothing to show that 5 or 6 minims of epinephrine do not stop uterine contractions.

"It is the authors' impression from clinical observations, that no advantage is obtained from the use of epinephrine in contraction rings. This opinion is based on both abdominal palpation and vaginal examination of patients treated with epinephrine." A constriction ring can be suspected from the character of the "pains" and from the lack of progress, but cannot be diagnosed without introducing the hand into the uterus and feeling it. If you cannot know of the presence of the ring without actually feeling it, how can one judge the effect of adrenalin on this ring by abdominal or vaginal examination. On the other hand, if the patient is anesthetized sufficiently for you to attempt to introduce your hand into the uterus, and you are unable to do so on account of a constriction ring, and without changing the depth of the anesthesia 5 or 6 minims of adrenalin are now given intramuscularly, and in a few minutes you feel the ring disappear and you are able to deliver the baby either by version and extraction or by forceps, you have clinical evidence that epinephrine relaxes the constriction ring. This has happened to me not once but ninety-one times. Twice the ring did not relax.

As to the potential risk of giving epinephrine to a fatigued, dehydrated and shocked patient who is in the excitement phase of ether anesthesia, I have no experience. In the first place I certainly would not give ether to such a patient. In the second place, I would not attempt to make an intrauterine examination when the patient was in the excitement phase of anesthesia. However, there is no evidence that epinephrine would do any harm to such a patient.

M. PIERCE RUCKER, M.D.

Medical Arts Bldg.
Richmond, Va.
June 11, 1943.

Transportation of Semen Specimens

To the Editor:

The customary methods of determining the motility of the male sperm is for the specimen to be collected from the inseminated vagina or from a condom. The fault of the first procedure is that the volume of ejaculate cannot be accurately measured. The wearing of a condom in the axilla to the doctor's office is undesirable.

The suggested method is to permit the condom to slide off and remain in the vagina after intercourse. The neck is knotted and a pad worn to prevent the specimen from dropping out. In this way, the exact amount, consistency and motility can be measured; and the optimum temperature of the vagina will protect the sperm. Of course, the effect of the washed rubber on the viability cannot be avoided.

1314 Bryant Bldg.
Kansas City, Mo.
May 20, 1943.

LEO H. POLLOCK, M.D.

American Journal of Obstetrics and Gynecology

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No. 3

Original Communications

SUPERFICIAL NONINVASIVE INTRAEPITHELIAL TUMORS OF THE CERVIX

RICHARD VAN DYCK KNIGHT, M.D., NEW YORK, N. Y.

(From the Department of Pathology, The Sloane Hospital for Women)

IN REVIEWING the reports on the early diagnosis of genital carcinoma, a significantly increasing number of early superficial epitheliomata of the cervix is noted.

Our interest in this problem has been stimulated recently by the occurrence, on our gynecologic service, of several early noninvasive epitheliomata of the cervix. With the problem of early diagnosis in mind, all the material on file of lesions of the cervix was carefully reviewed. In every instance in which the old microscopie slides revealed suspicious or interesting changes, the original blocks of tissue were recut. Often serial sections were made and in one instance the tissue was re-embedded in order to obtain better orientation of the tissue. The clinical records of these cases were also carefully studied.

From January, 1927, through April, 1943, four hundred and six primary squamous cell epitheliomata have been observed on the gynecologic service. Of these four hundred and six cases, seventeen were early, superficial lesions. In ten cases the diagnosis was made from the examination of enrettings from grossly normal appearing cervixes in individuals with fibromyomata or chronic inflammatory disease of the adnexa. In only two cases were minute gross lesions of the cervix noted clinically and both were interpreted as papillary erosions. In two instances the disease had its origin in cervical polyps.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

Case Reports

Case 1.—*Unit No. 78502.* This case is presented in considerable detail because of its unusual interest.

The patient was first seen in October, 1927, because of irregular vaginal spotting. She was 55 years of age. She had had a supravaginal hysterectomy in 1910. Examination revealed a large, red, granular cervical polyp, protruding from the external os, which bled easily on manipulation. This was avulsed and the base was curetted.

Sloane Pathology No. 2457. Microscopic sections of tissue revealed an irregular, somewhat fragmented polypoid structure composed of delicate, rather edematous fibrous connective tissue. In several areas the surface was covered by a single layer of tall, cylindrical epithelium typical of the cervical mucosa. These cells appeared uniform in size and shape. The lining epithelium dipped into the subjacent stroma at irregular intervals to form numerous typical compound racemose glands, a few of which were dilated and cystic. The most striking feature of the lesion, however, was the presence of broad sheets of squamous epithelium which covered many portions of the surface of the polyp. Due to poor orientation of the tissue and obliquity of section, these bands of squamous cells appear in some regions to lie within the stroma. This is an artefact. These sheets of epithelium have no resemblance to the usual squamous metaplasia often seen in polyps. The cervical mucosa is often replaced by squamous cells, but invasion of the stroma is not seen.



Fig. 1.—(Case 1.) Low power view of cervical polyp showing extensive squamous metaplasia (X5).

These sheets of cells present a marked hypertrophy of the Malpighian zone. No evidence of stratification is present, the individual cells being piled one on another in a haphazard fashion. Acanthosis is minimal and everywhere the basement membrane is intact. The subepithelial stroma is quite vascular and slight to moderate infiltration of lymphocytes and plasma cells is noted. The basal cell layer appears relatively normal with the usual palisading pattern. However; the cells immediately above

this zone and extending up to the surface, present striking alterations. They have lost their normal orientation. They vary considerably in size, shape, and staining quality; nuclear patterns are variable. Two to four mitoses are seen in the high power fields. Deformed, bizarre, hyperchromatic nuclei, surrounded by clear spaces, are present. The individual cell outlines are indistinct, due to inter- and intracellular edema. Because of tangential section, a few round, or oval, plaques of these atypical squamous cells, seem to radiate around central clear spaces. (Figs. 1 and 2.)

Because of this interesting pattern, the original paraffin blocks were melted and the tissue was re-embedded, in an effort to acquire a more accurate orientation of the tissue. This met with only partial success.

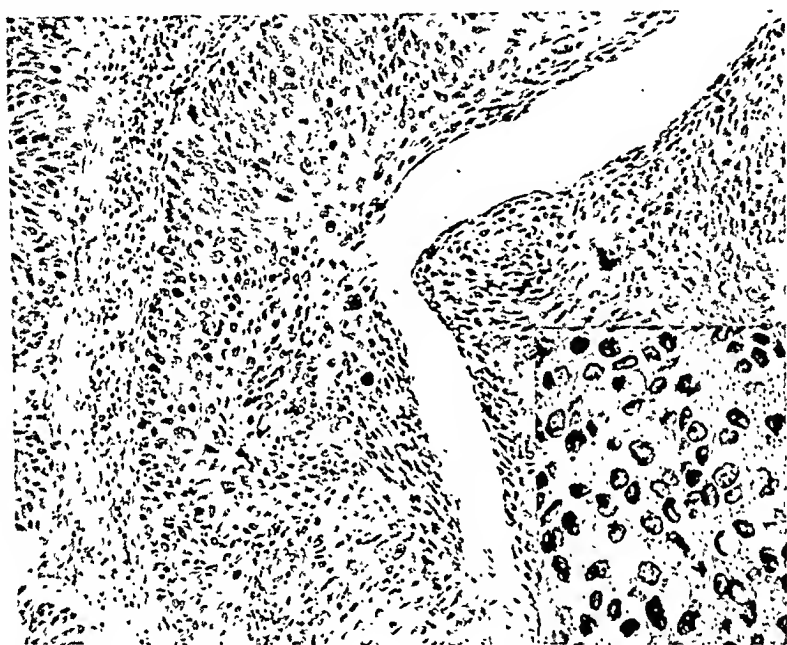


Fig. 2.—(Case 1.) High power view of polyp showing disorderly cellular arrangement in areas of metaplasia ($\times 150$). Insert reveals superficial resemblance to Bowen's disease ($\times 300$).

The patient remained well until January 16, 1929, when she was seen again because of a blood stained vaginal discharge of two months' duration. Examination under anesthesia revealed a somewhat contracted vaginal vault. The cervix was difficult to visualize. The mucosa presented a bright red, superficial, granular appearance. Bleeding occurred easily on manipulation. The tissues felt soft and pliable and presented none of the characteristics of epithelioma. On January 19, 1929, a biopsy of the cervix was done and scrapings from the granular surface were taken for examination.

Sloane Pathology No. 3192. Microscopic sections of cervical biopsy revealed a single ovoid plaque of dense fibrous tissue, one surface of which was covered by a band of squamous epithelium presenting all the characteristics of a noninvasive epithelioma. The scrapings from the vaginal vault revealed numerous strips of squamous epithelium, all showing the above described pattern.

The vaginal discharge continued. On March 11, 1930, cervical stump was noted to be small, atrophic, freely movable. The canal measured

2 cm. Posterior to the cervix was a bright red granular area which was divided by a ringlike contracture of vaginal mucosa. This tissue bled easily but did not feel thickened. Mucosa was soft and pliable. The tissue readily peeled off, like granulation tissue. One hundred milligrams of radium were left in this region for six hours. The lesion on the vaginal vault looked the same as before, except for lateral extension.

Sloane Pathology No. 4159. Microscopic sections of tissue revealed numerous broad strips of atypical squamous epithelial cells showing the same abnormal features described above.

On May 5, 1930, patient was given 400 mg. hours of radium. On October 8, 1930, it was noted that the patient was asymptomatic. The vaginal vault was occluded. On May 5, 1931, the patient had a sudden gush of fluid from vagina.

Examination on September 1, 1931, revealed a small opening in the occluded vaginal vault. On dilating this, the opening was found to lead to a small smooth lined cavity. No evidence of carcinoma noted. A biopsy was taken.

Sloane Pathology No. 5475. Microscopic section revealed a small piece of edematous connective tissue on which was superimposed a strip of squamous epithelium presenting changes from the normal as described above.

December 4, 1931, asymptomatic. No bleeding or discharge. Small opening in vaginal vault. May 13, 1933. Recurrence of serosanguineous discharge preceded by profuse vaginal bleeding. The constriction below the vault was firmer. No ulceration was seen.

October 5, 1933, biopsy of ring and scraping from vault were taken. The tissue lining the pocket was soft, pliable. Seventy-five mg.-hours of radium given. Sloane Pathology No. 7448. Microscopic sections of biopsy revealed the same type of squamous epithelium except that now slight invasion of subjacent stroma is noted. X-ray therapy was begun.

October, 1934, a recurrence of the vaginal discharge was noted. January 7, 1935, condition unaltered. Patient refused more radium.

April 11, 1935, biopsy of vault and 50 mg. of radium inserted for 49 hours. Sloane Pathology No. 9019 presents identical picture of previous biopsy.

When last heard from in 1938, the mild bladder and rectal symptoms, which were thought to be due to radium, were subsiding.

Case 2.—Unit No. 512001. A 65-year-old white gravida vii, whose menopause occurred twelve years previously, was first seen in March, 1937, because of vaginal bleeding for three months. Examination revealed a cervical polyp. At operation March 26, 1937, this structure, the cervix and adjacent vaginal mucosa revealed a superficial, bright red granular lesion which was easily removed with a curette, leaving a dull red moist surface. On April 13, 1937, patient received 70 mg. of radium for 100 hours. She was last seen in the follow-up clinic November 13, 1942, at which time patient was asymptomatic. The vaginal vault was contracted and the mucosa appeared normal.

Sloane Pathology No. 11130. Microscopic sections from curettings, from vagina, cervix, cervical canal revealed a similar pattern. Many irregular strips and plaques of abnormal stratified squamous epithelium were present, along with fragments of cervical mucosa and small fragments of fibromuscular tissue. The curettings from fundus consisted only of cervical epithelium showing squamous metaplasia or epidermi-

zation. All pieces of squamous epithelium, including scattered areas of squamous metaplasia from the polyp, showed uniformly abnormal changes, resembling an epithelioma. No pearl formation is seen anywhere. No involvement of the fibromuscular tissue was present and only the surface of the polyp was involved.

Case 3.—Unit No. 700876. A 50-year-old para ii, gravida vii, was admitted because of postmenopausal vaginal spotting of two years' duration. The menopause occurred six years ago. During the past two months she noted frequent episodes of bright red spotting.

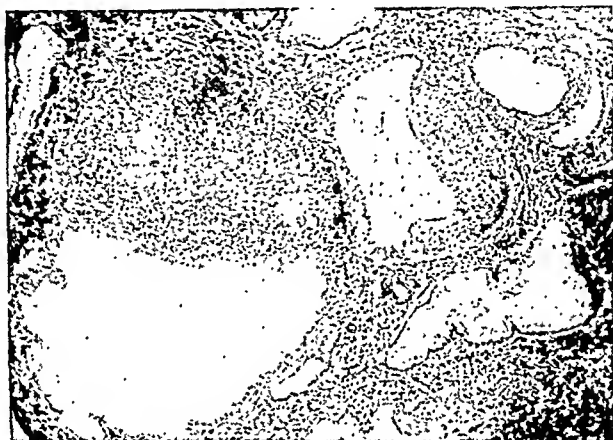


Fig. 3.—(Case 3.) Low power view of cervical biopsy showing extensive metaplasia ($\times 80$).

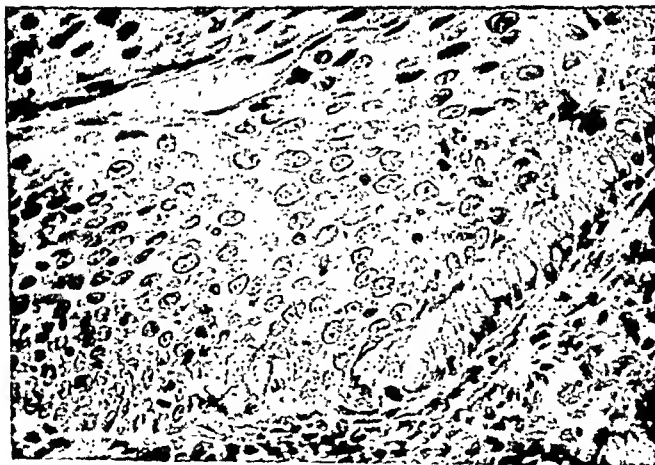


Fig. 4.—(Case 3.) High power view of details of metaplastic changes ($\times 200$).

Examination at time of curettage and biopsy of cervix on March 9, 1943, revealed a 3 mm. area just within the external os of the cervix which was granular, red, and presented small white papules, pinpoint in size. This area was excised in toto.

Sloane Pathology No. 18976 revealed marked squamous metaplasia of cervix with neoplastic alterations of the epithelium tending toward a Bowenoid pattern.

One week later, another biopsy was taken and radium inserted. The second biopsy failed to reveal any squamous epithelium. Apparently the entire lesion had been removed at the first operation.

The patient was given 6,000 mg.-hours of radium. (Figs. 3, 4 and 5.)

Case 4.—Unit No. 229808. A 53-year-old white woman was admitted because of intermittent vaginal spotting and watery discharge of two years' duration. Menopause occurred at 48 years of age.

On December 30, 1936, a curettage was done. Inspection of the cervix revealed an old deep laceration with one very small, slightly raised eroded area. A foul discharge was present.

Sloane Pathology No. 10867. The curettings from the fundus were normal. Tissue removed from the cervix with a curette revealed normal cervical mucosa with a dense stroma. In several areas the surface of the tissue was covered by atypical squamous epithelium and in one region a round plaque of squamous cells was seen just beneath the surface. Hyperplasia of the Malpighian zone was striking. The cells had lost their usual tendency toward stratification and varied moderately in size and shape. Mitoses were frequently noted.

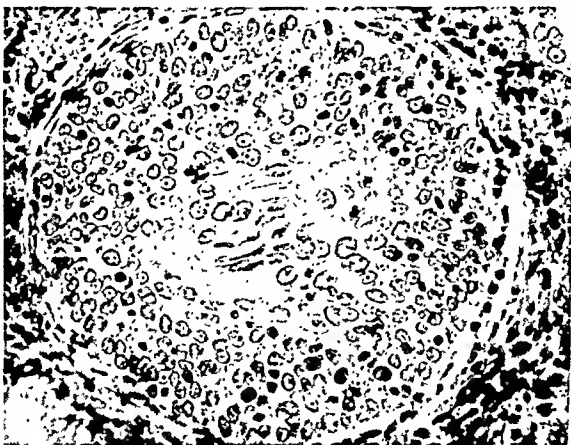


Fig. 5.—(Case 3.) High power view of cervical gland entirely replaced by squamous epithelium showing characteristic epitheliomatous changes ($\times 150$).

Patient was followed closely in the clinic where she was treated vigorously with estrogenic substances weekly, and douches because of senile vaginitis which manifested itself by a foul yellow vaginal discharge and occasional spotting.

She was last seen in May, 1931, and was asymptomatic. Her local condition had improved and no abnormalities were found on examination.

Case 5.—Unit No. 408675. The patient, aged 45, was admitted on November 3, 1939, because of metrorrhagia. In 1934, she had a curettage, amputation of cervix and repair of rectocele. The curettings revealed cystic glandular hyperplasia. Review of cervical tissue showed a superficial noninvasive epithelioma.

Sloane Pathology No. 8054. Microscopic sections of cervix revealed moderate squamous metaplasia involving some of the glands. The surface presented an area covered by abnormal squamous epithelium, revealing loss of stratification, disorientation of cells, 2 to 3 mitoses

per high power field, and moderate hyperplasia and hyperchromatic variable nuclei.

During 1938-1939, she received stilbestrol.

On examination on November 3, 1939, a small granular erosion of the cervix was noted. The cervix was biopsied.

Sloane Pathology No. 14267. Microscopic sections of tissue revealed strips of normal squamous epithelium, among which were several that presented hyperplasia, disorderly cellular arrangement, mitoses and nuclei varying markedly in size, shape and staining reaction.

On December 8, 1939, patient was readmitted and another biopsy was taken which showed only normal epithelium.

Patient was seen once in 1940, at which time she was asymptomatic and her physical findings locally were negative.

The entire lesion was apparently removed at the biopsy done on November 3, 1939.

Case 6.—Unit No. 280378. A 40-year-old colored woman, para v, gravida viii, was admitted on July 8, 1942, because of vaginal bleeding. On April 24, 1942, she had a curettage for incomplete abortion. Since then she has been spotting and her last period was quite profuse.

On July 10, 1942, a curettage was done. The cervix appeared eroded and a small 8 mm. fragment of tissue was removed. Sloane Pathology No. 18123. Microscopic sections of tissue revealed a small plaque of closely packed atypical squamous epithelial cells showing many mitoses.

On July 29, 1942, another biopsy was taken and 7,000 mg.-hours of radium given. Sloane Pathology No. 18188. Microscopic sections revealed no evidence of carcinoma in this second piece of cervical tissue. Apparently all disease had been removed.

March 19, 1943, no recurrence. No symptoms.

Case 7.—Unit No. 252697. A 28-year-old para i, gravida iii was admitted on November 28, 1939, because of abdominal pain, menorrhagia and metrorrhagia. She had a diagnostic curettage in 1931 for metrorrhagia. A normal endometrium was found.

A dilatation and curettage, and supravaginal hysterectomy were performed.

Sloane Pathology No. 14335. Among the curettings of normal endometrium were found several strips of stratified squamous epithelium revealing hyperplasia, loss of orientation of the individual cells, variation in size, shape and staining quality of the cells and their nuclei.

On January 10, 1940, a curettage and conization of the cervix was performed. Sloane Pathology No. 14472. Microscopic sections revealed abnormal squamous epithelium showing above-mentioned changes. (See Fig. 6.)

On February 7, 1940, patient was readmitted and given 2,700 mg.-hours of radium.

She was last seen on January 31, 1941, when she was asymptomatic and physical findings were negative.

Case 8.—Unit No. 367298. A 37-year-old colored para iii, gravida iii was admitted on January 21, 1933, because of abdominal pain of one year's duration and metrorrhagia for eight months. Examination revealed a badly lacerated and eroded cervix and a multinodular uterus the size of a three months' pregnancy.

A curettage, supravaginal hysterectomy, left salpingo-oophorectomy and right salpingectomy were performed.

Sloane Pathology No. 6786. Among the curettings were numerous broad strips of undifferentiated, atypical squamous epithelium. A few fragments of cervical glands were present showing metaplasia by a similar type of squamous epithelium.

Three weeks later the patient was given 5,000 mg.-hours of radium.

During 1934, 1935 and 1936, she received considerable x-ray therapy. Repeated follow-up examinations revealed a slowly progressive induration of the pelvis. She died in December, 1936.

Case 9.—Unit No. 691020. A 37-year-old white para vi, gravida vi was first seen in 1929 because of metrorrhagia for three months.

Examination revealed a firm, clean cervix and a slightly asymmetrically enlarged, firm uterus.

A curettage, supravaginal hysterectomy and perineorrhaphy were performed.



Fig. 6.—(Case 7.) Low power view of lesion showing epidermidization and superficial epithelioma ($\times 150$).

Sloane Pathology No. 3621. Microscopic sections of curettings revealed large pieces of fibromuscular tissue, scattered throughout which were round and oval strips of atypical squamous epithelium which had almost entirely replaced all the cervical glands. Portions of the surface of the tissue were covered by a similar atypical epithelium.

Three weeks later she was given 2,400 mg.-hours of radium and this was followed up by deep x-ray therapy. She was seen last in 1942, at which time she was well and free of recurrence or metastases.

Case 10.—Unit No. 601602. A 45-year-old white para o, gravida i, was first seen in March 1941, because of menorrhagia and intermenstrual spotting of six months' duration.

On March 7th a curettage, biopsy of cervix and supravaginal hysterectomy were performed. The cervix was found to be deeply lacerated and eroded. The uterus was multinodular and the size of a three and one-half months' pregnancy.

Sloane Pathology No. 16110. Microscopic sections of cervical biopsy revealed marked squamous metaplasia of the cervix, showing many atypical features and very superficial invasion of stroma.

On March 20th, the patient was given 4,000 mg.-hours of radium. Subsequently she has had considerable radiation therapy.

When seen in March, 1943, she was well without evidence of recurrence.

Case 11.—Unit No. 308859. The patient, a 49-year-old colored para ii, gravida ii, was first seen in December, 1940, because of backache and menorrhagia for six months. Examination revealed a normal appearing but lacerated cervix. The uterus was irregularly enlarged.

A curettage, supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed.

Sloane Pathology No. 15784. Sections of curettings revealed typical squamous metaplasia of the cervix with definite epitheliomatous alterations both in cell pattern and the individual cells.

Six weeks later the patient was readmitted. The cervix appeared normal. A biopsy was taken and 4,000 mg.-hours of radium were given.

Sloane Pathology No. 16003 revealed a typical squamous cell epithelioma involving the cervical glands and resembling the previous curettings.

Subsequently this patient has received considerable deep x-ray therapy.

She was last seen in January, 1943, feeling well and free of local recurrences.

Case 12.—Unit No. 621585. The patient, a 42-year-old white para o, gravida ii was admitted for operation because of menorrhagia. Examination revealed a multinodular fibroid uterus the size of a four months' pregnancy. Grossly, the cervix appeared normal.

On September 10, 1940, a curettage, amputation of the cervix, supravaginal hysterectomy and left salpingo-oophorectomy were performed.

Sloane Pathology No. 15459. Among the curettings were numerous large strips of very atypical squamous epithelium. Sections of the cervix revealed extensive squamous metaplasia showing epitheliomatous changes.

One week later, the patient was given 5,000 mg.-hours of radium.

To date she has remained well and is free of local recurrence or distant metastases.

Case 13.—Unit No. 371492. A 33-year-old colored para o, gravida o was first seen in April 1933, because of a lump in her abdomen, menorrhagia and dysmenorrhea, for one year. Examination revealed a large multinodular uterus the size of a four and one-half months' pregnancy. The cervix appeared normal.

On April 14, 1933, a curettage, supravaginal hysterectomy, excision of vaginal cyst were performed.

Sloane Pathology No. 6990. Among curettings were noted several strips of atypical squamous epithelium.

On May 2, 1933, a biopsy of the cervix was performed. Examination revealed a typical squamous cell carcinoma in areas of metaplasia.

On May 3, 1933, the patient received 5,000 mg.-hours of radium.

Following radiation therapy she developed a pelvic cellulitis and vesicovaginal fistula. This was repaired.

She was followed closely and, in all, three unsuccessful attempts to close the fistula were undertaken.

No evidence of local recurrence of the carcinoma was noted.

In September, 1942, the patient died at Harlem Hospital of "intestinal obstruction."

Case 14.—Unit No. 664265. A 46-year-old white woman, para 0, gravida ii, was admitted for menorrhagia of two years' duration.

On January 5, 1942, a curettage and excision of the cervix were performed.

Surgical Pathology No. 80798 revealed an abundant secretory endometrium. Among curettages were noted several large plaques of atypical squamous epithelium showing hyperplasia, hypertrophy, loss of orientation and stratification. Two to four mitoses were seen, per high power field. Variation in size, shape and staining quality of the cells and nuclei was frequently seen. The tissue from the cervix revealed a small plaque of intact surface epithelium showing the same changes without any tendency toward invasion. This was considered by Dr. A. P. Stout to be a Bowenoid type of superficial epithelioma.



Fig. 7.—(Case 15.) Low power view of cervix. At left is seen the normal epithelium of the portio. The cervical canal is entirely lined by squamous epithelium. In the middle of the picture the epithelium alters abruptly and becomes transformed into a superficial epithelioma seen on the right ($\times 70$).

On April 8, 1942, a biopsy was taken and 5,000 mg.-hours of radium given.

Sloane Pathology No. 17746 revealed surface epithelium of portio vaginalis showing above described changes.

January 14, 1943 follow-up. Occluded vault of vagina. No symptoms. No evidence of recurrence.

Case 15.—Unit No. 702514. A 38-year-old colored para i, gravida iii was first seen in April, 1943, because of enlarging abdominal mass of two and one-half years' duration. For the last year, there were periods of profuse bleeding every 2 to 4 weeks. Examination revealed a grossly normal cervix and a multinodular uterus the size of a three and one-half to four months' pregnancy.

On April 6, 1943, a complete hysterectomy and bilateral salpingo-oophorectomy were performed.

Sloane Pathology No. 19070. The uterus, tubes and ovaries were not remarkable. Grossly the cervix appeared normal. However, on examination of the microscopic sections the normal squamous epithelium of the portio vaginalis was found to extend up into the cervical canal for its entire length, replacing the columnar epithelium entirely. A distinct change in the epithelium had occurred. The notable changes included loss of stratification and orientation of the cells, with variation in cell and nuclear size, shape and staining qualities. Narrow tongues of epithelium dip deeply into the stroma. In one area, abnormal squamous cells lie free, close to the surface. Early pearl formation is seen in one area. Serial sections of the entire cervix revealed the same lesion throughout the tissues, with practically no invasion.

The patient will be given deep x-ray therapy. (Figs. 7 and 8.)



Fig. 8.—(Case 15.) High power view of portion of tongue of atypical squamous epithelium seen in Fig. 8 at right, dipping deeply into the stroma ($\times 300$).

Case 16.—Unit No. 705653. A 45-year-old white nullipara was first seen in April, 1943, because of menorrhagia and slight metrorrhagia. Examination revealed no abnormalities.

A curettage was performed. The curettings from the cervix were unusually abundant. For this reason 50 mg. of radium was inserted.

Sloane Pathology No. 19047. Cervical curettings revealed abundant tissue composed of cervical glands showing marked metaplasia. In several discrete isolated areas atypical squamous epithelium lay in between the glands in the stroma, and early pearl formation was seen. Squamous metaplasia, of an atypical type, was prominent. The endometrium was hyperplastic and showed some cystic changes.

The patient received 6,000 mg.-hours of radium.

Case 17.—Unit No. 707686. A 43-year-old colored para ii, gravida iii was first seen in March, 1943, because of enlarging abdominal mass for two years. Except for one recent episode of menorrhagia, she has had no abnormal bleeding. Examination revealed a lacerated infected cervix and a large multinodular uterus the size of a five months' pregnancy.

On March 30, 1943, a curettage, complete abdominal hysterectomy and bilateral salpingo-oophorectomy were performed.

Sloane Pathology No. 19042. The curettings were abundant. On microscopic examination the tissue was seen to be composed almost entirely of cervical glands, revealing striking squamous metaplasia which appeared frequently very atypical, with many abnormal cells and early pearl formations. The cervical glands were rather hyperplastic. Serial sections of the cervix revealed that almost all the mucosa had been removed with the curette. Only in one or two areas were there noted, on the surface, small nests of squamous epithelium. The lining epithelium of the portio was normal. About midway up the cervical canal, was found a single localized patch of atypical epithelium dipping deeply into the stroma. Nearby were several small nests of atypical squamous epithelium lying in the connective tissue stroma. The histopathology of this case bears a marked resemblance to Case 15.

The patient will receive deep x-ray therapy.

Discussion

Of the seventeen cases of early superficial epitheliomas of the cervix, the average age incidence was 44.1 years. Symptoms covered a span of three months to two and one-half years, the average duration being 14.2 months. The presenting symptom in this group was variable. In many cases, there were absolutely no symptoms which might arouse suspicion of an epithelioma. Eleven of these cases had irregular intermenstrual bleeding. The remaining six patients' complaints included profuse menstrual bleeding, abdominal mass, and dysmenorrhea. The presence of a carcinoma was completely unsuspected in eleven cases.

Additional pathology included two cases with polyps, and nine with fibroids. Both of these conditions are capable of producing abnormal vaginal bleeding.

Case 1 of this Group is of especial interest because of the prolonged course and superficial involvement. The occurrence of malignant change in cervical polyps is unusual. The rarity of this lesion is attested to by the sporadic case reports of such transformations. The nature of the original lesion in this case was overlooked. A two-year latent period ensued without symptoms. A correct diagnosis was finally arrived at, only after repeated biopsies had been taken. Throughout the course the lesion remained superficial and spread laterally. In reviewing the material on this case, it was suspected that the lesion might be Bowen's disease. However, on careful study and serial sectioning, the resemblance to Bowen's disease was found to be superficial. The response of a lesion of this type to inadequate doses of radium is well illustrated by the clinical course.

Case 2 resembles the first case in many respects. The lesion apparently began in a polyp and spread laterally. This patient received 7,000 mg.-hours of radium and has been free of symptoms and recurrence now for six years.

Cases 4 and 5 received no therapy other than biopsy. The lesions were small but definite. Probably the entire lesion was removed in both instances. Both of these patients were followed for five years but have been lost subsequently.

Case 6 is of interest inasmuch as the patient probably had this early epithelioma at the time of her spontaneous abortion. Danforth³ has reviewed the subject of pregnancy complicated by cervical carcinoma and points out that not infrequently spontaneous abortion occurs.

Cases 7 through 13 inclusive had a supravaginal hysterectomy and Cases 15 and 17 had a complete hysterectomy. Only three of these patients complained of intermenstrual bleeding. All had fibroids. In the three cases where the cervixes were notably diseased, two complete hysterectomies, a cervical amputation, and supravaginal hysterectomy were done. Clinically, carcinoma was unsuspected in these cases. Fortunately, in each instance, a preliminary curettage of the cervix as well as of the endometrial cavity were performed. Again, grossly there was nothing suspicious about the curettings. Had a supravaginal hysterectomy been performed without a curettage, these patients would have returned subsequently and been classified as carcinomas of the cervical stump.

All these patients received radium in doses varying from 2,400 mg.-hours to 7,000 mg.-hours. This was followed by deep x-ray therapy. Case 8 lived only three years, dying of massive extension throughout the pelvis. Case 13 lived for nine years. She had had considerable deep x-ray therapy and a persistent vesicovaginal fistula, probably from a radium burn. Clinically, there was never evidence of recurrence. She was taken to Harlem Hospital where a diagnosis of intestinal obstruction was made. Operation was refused.

Although many of the cases are rather recent, it appears from the follow-up of the earlier cases that these superficial epitheliomas develop slowly and are relatively benign, as compared with the more obvious larger lesions involving the portio vaginalis. The site of all of these lesions was just at or within the internal os. In Cases 15 and 17, the lesions were well up in the cervical canal. The presence of squamous epithelium in cervical tissue is not uncommon in chronic cervicitis and polyps of long standing.

This question of squamous metaplasia or epidermidization of the cervical mucosa is of considerable interest. Robert Meyer's original work on congenital erosions of the cervix and the embryology of the cervix and vagina,⁵⁻⁶ has thrown considerable light on the subject and has aided pathologists in explaining the presence of squamous epithelium in cervical glands. Meyer has demonstrated small nests of squamous epithelial cells from the basal zone lying just beneath the cylindrical cervical epithelium in both adults and young children. He has demonstrated the fact that during the third and fourth months of

fetal life, the cervix presents squamous epithelium throughout at least two-thirds of its length. It is not until the sixth month of fetal life that the columnar epithelium replaces the squamous cells. A reversal of this interplay of epithelial cells occurs again in infancy and childhood, and it is not until puberty that the cervix is finally covered throughout by columnar epithelium. During these cyclic alterations, small nests of squamous cells from the basal layer might well become trapped and lie dormant for variable periods of time until trauma, infection, or some other stimulus resulted in active growth. Meyer believes that all types and degrees of squamous metaplasia can be explained on this basis. Many authors have considered squamous metaplasia as a stage in the process of healing of cervical erosions.^{1, 2, 5-7} However, only a small percentage of cervical erosions reveal metaplasia. Another possibility in the etiology of squamous metaplasia, is the upward extension of strands of squamous epithelium from the portio following trauma. Evidence for this mode of development has not been well substantiated. A third possibility is the direct transformation of columnar epithelium to squamous epithelium. This process has been noted in advanced chronic inflammatory processes elsewhere in the body. The evidence to date seems to favor the first and third of the theories. Ribbert,⁹ in discussing epidermidization of the cervix, favored this process as the origin of the majority of squamous epitheliomas of the cervix. Within recent years, this process has been considered benign. In the majority of cervices showing squamous metaplasia, there is little to suggest carcinoma, when one notes the orderly cellular arrangement and uniformity of the cells. Undoubtedly the increased interest in the early diagnosis of cervical carcinoma has led to more thorough care in handling chronically infected and lacerated cervices presenting this metaplastic change. This, in turn, has resulted in the eradication of a pathologic process which has the potentialities of carcinogenesis.

Among 459 polyps from the Sloane gynecological service, fifty-three showed evidence of metaplasia. Of these, only two were malignant. Since 1927, the diagnosis of squamous metaplasia of cervical tissue has been made 232 times. In none of these lesions, except those cases herein reported, was there any evidence of carcinoma. Thirteen of our cases of early, superficial epitheliomata are in areas of squamous metaplasia. The evidence substantiates Wollner's⁸ belief that this process is not as benign a lesion as it has seemed to many investigators in recent years.

In none of the cases reported in this paper was there found any deep invasion. It is impossible to predict how long a latent period of intra-epithelial development and superficial surface spread will last, and when rapid growth and invasion will become manifest. Only one of our cases (Case 8) died of extension of the disease. The original tissue

showed malignant metaplasia in practically all of the cervical glands. Her symptoms had been present for one year.

It should be emphasized that the quantity of material removed from the cervical canal by curettage in chronically infected cervixes, which present epidermidization, is rather more abundant than one would expect. Curettings from normal or only mildly infected cervixes generally are scanty or absent, consisting of shreds of normal squamous epithelium or scraps of fragmented cervical epithelium and glands. It is possible that, with a thorough curettage, the entire hyperplastic and metaplastic cervical epithelium may be removed. Perhaps such therapy results in the removal of tissue which, if left in situ for a sufficiently long time, might develop into the typical epithelioma by stages of progressive metaplasia. We have recently observed one patient who had a curettage, supravaginal hysterectomy and bilateral salpingo-oophorectomy. The curettings consisted entirely of hyperplastic and metaplastic cervical glands which showed no epitheliomatous alterations. Six weeks after her operation, the cervical canal measured 2.5 cm. in length, and a curettage produced no tissue whatsoever. Had she not had a thorough curettage at her first operation, it is conceivable that in the future she might return with a cervical stump epithelioma. The appearance of the curettings in Cases 15 and 17, suggest that more than one area of metaplasia may develop into epitheliomata forming small, isolated, discrete lesions or multicentric foci of superficial cancer. When these lesions begin to develop rapidly, after a latent period of 18 to 24 months or longer, they may account for some of the more virulent, rapidly progressing epitheliomata of the cervix which do not seem to respond to radium. (See Case 8.)

Schiller,⁴ in his paper describing the iodine test, points out the latent period in the rate of growth of cervical epitheliomata. The early stage may last for long periods of time and then rapid development ensue. Squamous metaplasia may be the earliest phase of this process. Both Schiller and Schmitz, in discussing the former's paper,⁴ emphasize the distinct cytologic alterations that occur in an epithelioma before invasiveness develops. The latent period before invasiveness becomes manifest undoubtedly varies from patient to patient, depending possibly on local tissue resistance and other unknown factors.

As far as prevention and therapy are concerned, there is no doubt that when removal of a uterus is indicated, the complete hysterectomy, either by the vaginal route or from above, is the operation of choice, especially in the presence of a diseased cervix. Probably many of the stump epitheliomata reported were present at the time of supravaginal hysterectomy. When the diagnosis is made from biopsies, polyps, curettings or trachelorrhaphy tissue, the conventional use of radium and deep x-ray would seem to be the method of choice. Among 538 cervical epitheliomata on file in this Hospital, 38 or 7.1 per cent were stump carcinomata. Of these, three of the patients had supravaginal

hysterectomies here. Thirty-four per cent of these cases appeared within two years following hysterectomy. The cases which were discovered immediately are reported here.

Superficial noninvasive epitheliomata of the type characterized by this group of cases, present occasionally a superficial resemblance to Bowen's disease. On several occasions the term Bowenoid epithelioma has been used. However, on careful study of the microscopic sections many differences are found. The hyper- and parakeratosis is lacking. Although the Malpighian zone is hypertrophied, acanthosis is not usually present. Both lesions present a disorderly cellular pattern, but this group of cases does not show the characteristic nuclear clumping and numerous corps rondes found in Bowen's disease. These lesions, over a period of time, show invasiveness, as evidenced by violation of the basement membrane. In Bowen's disease this has not been described, even though the disease has been present for many months or years, unless a definite transformation into a typical squamous cell epithelioma has occurred.

It is evident that the cervix cannot be regarded as free of disease no matter how clean and apparently healthy it appears. Many of these lesions occurred within the cervical canal, completely out of sight in regions not accessible to the iodine test or the colposcope.

This study has emphasized again the importance of careful microscopic examination of all tissues removed at curettage or biopsy. The importance of curetting separately the cervix and uterine cavity, and the segregation of these curettings for embedding and cutting, as has been often mentioned by Hyman and Corsecaden, should be noted. No less important is the correct orientation of the tissue before fixation, and the frequent need for recutting blocks in order to visualize tissues at deeper levels.

Summary

Seventeen cases of superficial epitheliomata of the cervix have been reported.

Conclusions

1. Early superficial noninvasive epitheliomata of the cervix occur more frequently than supposed.
2. These lesions not infrequently have arisen in tissue which has undergone squamous metaplasia.
3. These lesions tend to develop slowly over a relatively long period of time and seem less malignant than the more obvious epitheliomata.
4. These lesions should be treated as vigorously as the more obvious epitheliomata whether by radiation or surgery, or a combination of the two.

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litter successfully as to maintain the maternal organism. Because the high mortality of nursing rats was considerably reduced by feeding the vitamin B complex to the young, Sure¹² concluded that the transfer of these vitamins into the milk is rather inefficient. In earlier studies he had shown that thiamine is the most important of the B-vitamins studied for the promotion of successful lactation, due to its capacity to stimulate appetite and copious milk flow. Shin¹³⁻¹⁵ studied the transfer of thiamine from the maternal tissues to the fetus and to the mammary glands of rabbits, rats and mice. A dietary partially deficient in thiamine caused the estrus cycle to become erratic or disappear. If conception occurred, abortion was likely. If the young were born alive, they showed symptoms of thiamine deficiency. It is not appropriate to review here all the literature based on animal experiments with thiamine during pregnancy. The evidence clearly indicates that pregnancy increases the thiamine needs and that rats may require perhaps five times as much thiamine for successful pregnancy and lactation as for growth.^{10-11, 16-18}

Strauss and McDonald¹⁹ reported that pregnancy unmasks latent beriberi in women and that the polyneuritis of pregnancy is probably a dietary disorder. Subjects with pregnancy eclampsia generally exhibit thiamine deficiency²⁰ which is accompanied by subnormal levels of thiamine in the placental tissues. Beginning with the fourth month of pregnancy Hildebrandt and Otto²¹ injected large doses of thiamine intravenously and were not able to measure significant amounts of thiamine in the urine of women until after the child had been born, indicative of rather severe thiamine inadequacy. A similar result is reported by Neuweiler²² who reported the retention of large proportions of parenteral doses of thiamine, especially when the subjects manifested "toxemia," again indicating thiamine insufficiency. Also, it has been shown²³ that 12 per cent of the pregnant women studied showed electrocardiogram evidences of thiamine deficiency. These citations from the clinical literature serve to show that evidence is slowly accumulating which indicates that the thiamine requirements of women in pregnancy are rather high.

Toverud⁶ observed that 46 per cent of the 114 pregnant women studied normally excreted no thiamine in a 24-hour urine sample. In eight of ten subjects given a test dose of 5 mg. no thiamine was detected in the urine by thiochrome assay. When four women were given 1 to 3 mg. daily for 5 to 17 days, no significant excretion was noted and it was necessary to give 4 to 5 mg. daily to produce as high an excretion as was measured in a nonpregnant control group. It was concluded that pregnancy had increased the thiamine requirements four- to fivefold. Similar tests on women who had been lactating two to four months, resulted in a higher excretion of test dosages of 5 mg. which was interpreted to indicate that the lactation requirements for thiamine are only slightly higher than those of nonpregnancy.

Methods for Measuring Thiamine Status

The literature discloses that the thiamine status may be measured by estimating the thiamine, pyrimidine or pyruvic acid content of the blood or urine, either with or without the administration of small or large test dosages of thiamine, given parenterally or by mouth, and that these compounds may be measured by colorimetric, fluorimetric, biologic or microfermentation procedures. When this research was

initiated (1940), a thorough study was made of these various possibilities and as a result a technique was evolved which, in our hands, produced reliable data. In this research the quantity of thiamine needed to produce the same excretion status on successive lunar months during late pregnancy and early puerperium was measured.

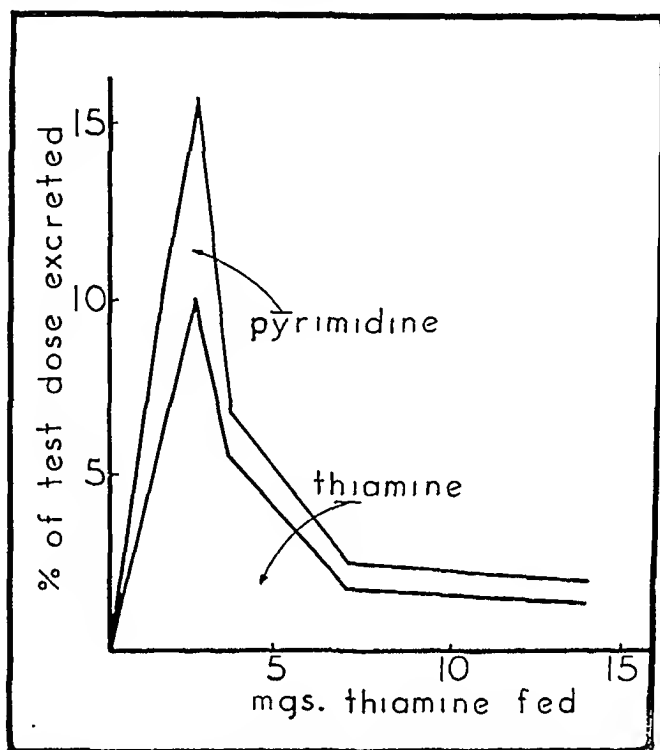


Fig. 1.—Excretion of test doses of thiamine expressed in terms of thiamine and thiamine plus pyrimidine. Pyrimidine excretion parallels thiamine excretion.

Experimental Procedure

Injection Series.—The subject is given a supper low in thiamine content at 5 P.M. At 8 P.M. she voids her urine, then collects all urine passed up to 7 A.M. on the following morning. Collections are made into two-liter bottles containing 10 c.c. of 10 per cent sulfuric acid, to hold the acidity of the urine below pH 4 and preserve the thiamine content for at least 48 hours. At 7 A.M. the pooled urine sample is taken to the laboratory and refrigerated (5° C. or less), then analyzed by the modified microfermentation procedure²⁴ to determine the thiamine and pyrimidine excretion during a basal eleven-hour period. It has been determined that the basal excretion is approximately the same from day to day when a subject is living on an institution dietary.

Having established the basal excretion, the same procedure is repeated on the following night. This time, however, the subject is given an intramuscular injection of thiamine solution. On successive nights these injections are progressively increased until urine analysis shows that the "excretion peak" has been passed, the excretion peak being the point at which the highest proportion of the administered thiamine is excreted (Fig. 1). At the end of each succeeding lunar month the basal excretion and excretion peak of the subject are again determined. The dosage is increased each month according to the

following schedule which was worked out on a preliminary group of twenty subjects:

LUNAR MONTH OF PREGNANCY	MG. THIAMINE TO BE INJECTED ON SUCCESSIVE DAYS					
	1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY
7	0	.25	.50	.75	1.00	1.25
8	0	.25	.50	.75	1.00	1.25
9	0	.50	.75	1.00	1.25	1.75
10	0	.75	1.25	1.75	2.50	5.00
PUERPERIUM	0	.75	1.25	2.50	3.00	5.00

Najjar and Holt²⁵ have shown that the major part of an intravenous injection of 1 mg. of thiamine is excreted within two hours, and that after four hours the excretion is nearly completed. McAlpine and Hills²⁶ found that when 1 mg. of thiamine was fed, the excretion was nearly completed in three hours. McInick and Field²⁷ have also observed a prompt excretion of test doses.

Ingestion Series.—The technique for ingestion studies is identical with that of the injection series, except that the thiamine is fed, preferably in tablet form. The dosages are increased on successive months and on successive days of each test period as follows:

LUNAR MONTH OF PREGNANCY	MG. THIAMINE TO BE FED ON SUCCESSIVE DAYS					
	1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY
7	0	0.5	1.0	1.5	2.0	2.5
8	0	0.5	1.0	1.5	2.0	2.5
9	0	1.0	1.5	2.0	2.5	3.5
10	0	1.5	2.5	3.5	5.0	7.0
PUERPERIUM	0	1.5	2.5	5.0	7.0	10.0

Details on This Study

In the present study the thiamine* used in the injection series was dissolved in physiological saline in concentrations of 1 or 10 mg. per c.c. The thiamine used in the feeding tests was fed in 1 grain tablets containing 1 or 5 mg. each. The potencies of these preparations were confirmed by the thiochrome method.²⁸

All of the fifty subjects used in this study were patients at the Florence Crittenton Home in Boston which receives primiparous unmarried women during the seventh lunar month of pregnancy or later. These subjects ranged in age from 14 to 22 years, but the majority were 18 years old. Women with disorders which might interfere with the absorption or metabolism of thiamine were excluded. Unfortunately, it was not possible to study these patients beyond the first puerperal month for they were discharged from the home and could not be further subjected to the strict control necessary for this type of study. Because it was not possible to study these subjects previous to admission, it was necessary that others be used as controls. Since the data show that the early pregnancy requirement is similar to that of nonpregnancy, our inability to study each subject during the entire gestation period is of no consequence.

The thiamine content of the food upon which the subjects subsisted during the investigation was determined each day by fluorimetric assay.²⁸ Food samples were collected by instructing the subject to

*We wish to acknowledge the generosity of Hoffmann-La Roche, Inc., in supplying the thiamine used in this study.

TABLE II. QUANTITIES OF THIAMINE BY MOUTH AND BY INTRAMUSCULAR INJECTION, REQUIRED TO PRODUCE THE EXCRETION PEAK IN SUBJECTS DURING ADVANCING PREGNANCY, AND IN NONPREGNANT CONTROLS. LACTATION PERFORMANCE WAS GRADED "GOOD" WHEN INFANT WAS ENTIRELY BREAST-FED UNTIL DISCHARGE, "FAIR" IF PARTIALLY BREAST-FED UNTIL DISCHARGE, AND "POOR" WHEN TAKEN OFF BREAST EARLY IN PUERPERIUM

SUB- JECT	NONPREG- NANCY	SUB- JECT	LUNAR MONTH OF PREGNANCY				LACTATION PERFORM- ANCE
			8	9	10	PUER.	
<i>I. Feeding Series</i>							
F. P.	0.25 mg.	R. L.		2.5 mg.	2.5 mg.	5.0 mg.	Good
M. N.	.50	M. B.		2.5	3.5	2.5	Poor
P. G.	.50	B. C.		1.5		3.5	Poor
E. W.	.50	P. E.			3.5	5.0	Poor
		P. M.			1.5	1.5	Poor
		M. L.		1.5	2.5	2.5	Good
		G. F.	2.5 mg.	2.5	5.0	4.0	Fair
		E. M.	1.5	1.5	2.5	2.5	Poor
<i>II. Injection Series</i>							
M. N.	0.10	L. K.	1.00	1.00	1.00	2.50	Good
V. T.	.10	L. S.	.75	1.00	1.00	1.75	Good
E. W.	.20	D. G.		.25	.50	.75	Fair
H. S.	.20	P. L.	.25	.50	.75	1.75	Poor
		N. H.		.75	1.25	1.75	Good
		M. H.		1.25		1.75	Good
		M. C.		.50	.75	.75	Fair
		M. W.			.50	.75	Poor

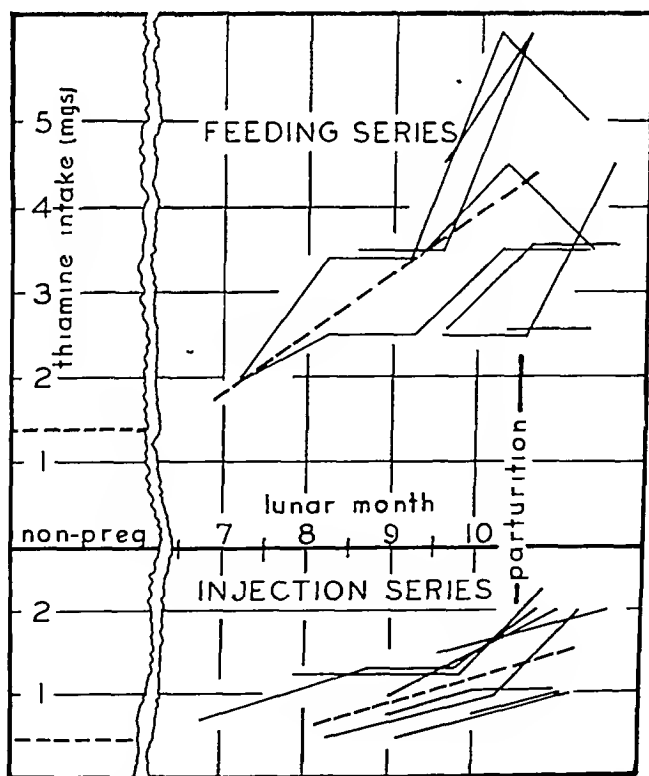


Fig. 2.—Data from Table II plotted with respect to parturition date and thiamine in food. Feeding series represent sum of food thiamine and thiamine fed as supplement while injection series represent calculated injection equivalent of food thiamine plus thiamine injected intramuscularly.

place on an extra plate, amounts of the food equivalent to that which she served herself at each meal. At the end of the meal this food (including milk and all thiamine-containing liquids) was placed in a collection bottle which was refrigerated until analyzed. The thiamine content of the daily dietaries varied between 0.24 mg. and 1.61 mg., and averaged 1.05 mg. and usually ran within 25 per cent of this average.

Discussion

The amounts of supplementary thiamine required to produce an excretion peak in nonpregnant subjects and at various stages of pregnancy are presented in Table II. Approximately one-third as much thiamine was required by intramuscular injection as by mouth to reach this peak in nonpregnant subjects, indicating that thiamine may be one-half as effective by mouth as by injection.

These data are presented in a more useful form in Fig. 2, by inclusion of the food thiamine. In the fed series, the sum of the food thiamine and the supplement represent the total thiamine which produced the excretion peak, and this sum has been plotted. However, in the injection series, thiamine was taken both orally and intravenously, and it has been shown above that thiamine is not equally effective by these routes. So that the results of this series might be evaluated, the amount of thiamine injected was added to one-third of that ingested by each subject, and the total daily thiamine intake is thus expressed in Fig. 2, as though all thiamine had been injected. It is evident in Table II, and Fig. 2, that the amount of thiamine necessary for the production of the excretion peak increased throughout the pregnancy period. In comparison with the nonpregnant control group, the relative increase was essentially the same in the injection series as in the fed series (Table III). Since the same results were obtained when thiamine was administered by two different routes, the above observation is significant and is a measure of a real increase in physiologic requirements. It is not, for instance, the result of an impairment of intestinal absorption resulting from the pregnancy state. Thus it appears that a woman in the tenth lunar month of pregnancy requires three times as much thiamine as in nonpregnancy to reach her excretion peak.

TABLE III. THIAMINE REQUIRED BY INTRAMUSCULAR AND ORAL ROUTES TO PRODUCE EXCRETION PEAKS IN PREGNANT AND NONPREGNANT WOMEN. RATIO OF THIAMINE REQUIRED TO PRODUCE EXCRETION PEAKS IN PREGNANCY, TO THAT REQUIRED IN NONPREGNANCY

PHYSIOLOGICAL STATUS	ROUTE OF ADMINISTRATION	
	ORALLY	INTRAMUSCULAR INJECTION
nonpregnant	1.0	1.0
7th lunar	1.4	--
8th lunar	1.8	1.8
9th lunar	2.6	2.5
10th lunar	2.9	2.9
1st puerperal	2.9	3.6

A typical excretion peak titration is shown in Fig. 1. The upper values represent the total of thiamine and pyrimidine excreted by the subject, while the lower graph presents the proportion of thiamine. It is evident that the excretion peak is a result of the combined effect of thiamine and pyrimidine.

The requirement for excretion peak seems to be the same, whether or not the subject is lactating. Human milk usually contains no more than 0.02 mg. of thiamine in 100 c.c.²⁹ A woman who had taken 3 mg. of thiamine as a daily supplement throughout the pregnancy period produced a milk containing 0.04 mg./100 c.c.,³⁰ but the 25 ounces which she secreted on the 18th postnatal day contained only 0.3 mg. of thiamine.

Although the loss by secretion in the milk is not very significant in terms of the total thiamine needs of the lactating woman, the requirements for milk synthesis may be considerable.

The excretion peak has been produced in all of the fifty-odd subjects studied, pregnant and nonpregnant, thiamine deficient and thiamine sufficient. Nonpregnant subjects with no clinical manifestations of thiamine deficiency and subsisting on a dietary of unvarying thiamine content require the same quantity as supplement from week to week to reach the excretion peak. Subjects showing thiamine deficiency require a larger supplement to attain the excretion peak. After the manifestation of deficiency has responded to thiamine therapy, small amounts of supplement are needed in this excretion test. Women in midpregnancy require slightly more thiamine than nonpregnant women and as pregnancy advances the amount of thiamine to titrate the peak becomes increasingly large. It is evident: (1) that the excretion peak is a normal physiological phenomenon; (2) that the quantities of thiamine needed for its titration are directly proportional to thiamine needs; (3) that this peak can be determined fairly accurately in a subject; and (4) that titration of the thiamine excretion peak is a useful method for (a) measurement of the effectiveness of thiamine therapy, or (b) measurement of relative increase in thiamine needs during physiological stress (such as pregnancy). At present it does not seem that this titration can be used to measure the actual quantity of thiamine needed by a subject, but rather the requirement relative to the normal.

Summary

The oral or intramuscular administration of thiamine to normal subjects causes the percentage excretion of thiamine and pyrimidine in the urine to increase as the dosage is increased on successive days until a peak is reached. Subsequent increases in dosage result in progressively less efficient excretion of thiamine or pyrimidine.

This excretion peak has been observed in all subjects studied, whether normal, thiamine deficient or pregnant. The quantity of thiamine required to titrate this peak appears to be proportional to the thiamine

status, is high for thiamine deficient persons and for women in advanced pregnancy and puerperium, and is low for those who are not deficient.

Thiamine was administered orally and intramuscularly to measure the excretion peaks of sixteen pregnant women. Since approximately three times as much thiamine was needed in titrating the excretion peaks of these subjects during late pregnancy and early puerperium, it is suggested that the requirements for thiamine during pregnancy and lactation are three times those of nonpregnancy.

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HEMORRHAGE AS THE MOST IMPORTANT CAUSE OF MATERNAL DEATH*

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THE number of puerperal deaths in the United States is steadily decreasing. In 1941,¹ the year for which the latest figures are available, the rate was 3.2 per 1,000 live births, or 48 per cent lower than 1933, the first year for which complete statistics were compiled. In 30 states the rate was lower, notably Montana (1.6), Washington (1.8), Utah (1.9), Minnesota (2.0) and Connecticut (2.0). The rate was highest in Florida (6.3) and South Carolina (6.2).

The reasons for this welcome reduction are not altogether clear. The trend has been downward since 1929, with sharper decline in the last five years. There can be no doubt that expansion of our national maternal welfare service has played an important part. A nationwide campaign of popular education has not yet reached every woman, and perhaps it is too much to expect that it ever will, though social and public welfare agencies, the radio and press are participating. Not all the information given the public has had merit but, on the whole, good has come of it. Continued education of the physician is, of course, a most important factor, for only when every one who practices obstetrics, consultant and general practitioner alike, can be made to feel that prevention of a single maternal death is an important contribution, will we approach the desired minimal mortality. The studies carried on by medical groups with the close cooperation of vital statisticians, have borne good fruit in many communities, and, I am sure, have had a profound effect upon our national death rate.

The rates for both white and Negro women have declined, but not uniformly. The rates for Negro women in 1940 and 1941 were nearly two and one-half times those of white women. In fact Yerushalmy² has shown that reduction of the rate in 1940 was accounted for entirely by reduction in the rate for white women. Since nearly one-quarter of the deaths in 1940 and 1941 occurred in Negro women, it is obvious that parallel reduction in the rates would effect substantial improvement in the total mortality. However, the high maternal death rates in southern states are not due to the racial factor alone, for the rates for white women are also higher than similar rates in other states.

Rates show significant decline even in large cities, where the racial factor might reasonably be expected to contribute unduly to maternal mortality. In 27 large cities, in half of which more than 10 per cent of the population was colored, the puerperal mortality rate for 1941 was considerably lower than the national rate.³ In New York City, where the rate from abortion is nearly seven times as high in Negro women as in the white, and the Negro puerperal death rate almost three times that of the white, the puerperal death rate in 1941 was 2.2 per 1,000 live births, a reduction of 50 per cent in ten years.

*Read, by invitation, at a meeting of the Boston Obstetrical Society, March 16, 1943.

Comparing our national figures for two five-year periods, 1931 to 1935, and 1936 to 1940, Yerushahny² finds that percentage reduction was greatest in the infection group (31 per cent) and lowest in the number of deaths due to hemorrhage and shock (16 per cent), with 24 per cent decrease in deaths due to toxemia. This resistance to reduction in the hemorrhage incidence deserves attention.

TABLE I. PUERPERAL MORTALITY, U. S.
PERCENTAGE REDUCTION 1931-1940

		WHITE	COLORED
Infection	31	34	20
Toxemia	24	27	12
Hemorrhage	16	16	8

Statistically infection is responsible for the greatest number of maternal deaths. In 1940, 41 per cent was assigned to this cause, 25 per cent to toxemia, and 23 per cent to hemorrhage, trauma and shock. This is not a complete or wholly satisfactory statement, for it refers to but 89 per cent of the deaths. The remaining 11 per cent was assigned to other and unspecified conditions largely because of inadequate data, though more than half occurred during or after delivery, the usual time for fatal hemorrhage.²

TABLE II. PUERPERAL MORTALITY, U. S., 1940

	PER CENT	NO. DEATHS
Infection	41	3626
Toxemia	25	2250
Hemorrhage, Trauma, Shock	23	2058
Unspecified	11	942

The principal reason for collecting and tabulating these vital statistics is to give us full knowledge of the problem. They are as valuable as the autopsy, since it is necessary to know what women die of before a satisfactory program of prevention can be undertaken. No problem can be solved until it is clearly stated.

Let us look a little more closely at these vital statistics upon which preventive programs depend. In at least 40 per cent, only one cause of death was reported. The accuracy of all the figures depends upon the character and quality of these vital records, yet this information varied widely throughout the United States. In New York and Massachusetts, for example, over 70 per cent of the certificates contained more than one cause, with 31 per cent showing three or more causes, while only 43.9 per cent in the East South Central States reported more than one cause, and only 12.8 per cent showed three or more. In many of the southern states there was an almost complete lack of detail on the certificates for Negroes.⁴

It is easy to code and tabulate causes of death when but one cause is reported, yet the result may be nothing more than mere arithmetic and of little value in planning well-rounded preventive programs. And even when two or more causes appear, there is still a problem, though a different one, for each death must be tabulated as if it were due to a single cause, and the additional information, valuable though it may be, is lost. It has been caused to disappear by the magic of rules and definitions which assign death to one statistical cause.

No one knows better than the obstetrician that maternal death is often the outcome of a complex sequence of circumstances, and rarely the result of one cause; that hemorrhage is a common and often a repeated incident along the way; that often infection would not occur at all, or that death would not follow it, if blood loss had not been considerable; that sepsis and hemorrhage are obstetric bed-fellows. Always an important factor, whether reported or not, hemorrhage is almost lost in tabulations. If general or local infection, pyelonephritis, thrombophlebitis or embolism and sudden death complicate the case, infection takes precedence over every other puerperal cause, no matter how serious, with the exception of ectopic pregnancy. Toxemia, too, is preferred over hemorrhage, unless placenta previa or placental separation is reported as well. Further, since 1940, deaths attributed to hemorrhage and trauma have been assigned to abortion, if they occurred before the twenty-eighth week of pregnancy, and not to their specific causes as formerly.⁵

Vital statisticians have become aware of the importance of investigating the frequency of contributory causes of death. In fact the Bureau of the Census in 1941, planned to tabulate one associated cause on all certificates reporting two or more joint causes of death. In 1936, there were 12,182 puerperal deaths, 1,398 of which were assigned to hemorrhage by the rules which provide for selection of one cause only. These were the published statistics. By tabulating only the first two causative factors, Janssen⁴ found that hemorrhage had been reported in 703 other cases, thus raising the total to 2,151. Approximately one-third of the cases in which hemorrhage had been reported were assigned to other causes. At the same time, however, all the deaths in which infection was mentioned, were coded under that heading.

TABLE III. PUERPERAL MORTALITY, U. S., 1936

12,182 DEATHS

1398 assigned to hemorrhage	
703 additional	
1635 assigned to accidents of labor	
3000 additional, assigned to	
hemorrhage	811
infection	1034
toxemia	786
embolism	336

Janssen⁴ showed, too, that 1,635 cases were formally assigned to accidents of childbirth, yet there were more than 3,000 additional cases reporting complications of delivery which had been variously tabulated under a single cause. Of these 1,034 were assigned to infection, 786 to toxemia, 336 to embolism and sudden death, and 811 to hemorrhage. When one recalls that accidents of childbirth statistically include injury during delivery, lacerations, inertia and atony of the uterus, as well as inversion and rupture, malpresentation and position, dystocia, prolonged labor, instrumental delivery, cesarean section, version and obstetric shock, an obstetrician need not exercise his imagination to estimate the frequency and importance of hemorrhage in the large number of cases tabulated otherwise. Here particularly the entire problem of joint cause selection is so difficult, so nearly impossible, that statistical

deductions as to the relative frequency and importance of hemorrhage and infection may properly be questioned.

In Brooklyn, too, all the major causes of death have shown notable decline.⁶ During the five-year period 1937 to 1941, the number of deaths fell from 164 to 79, and the puerperal mortality rate was reduced from 4.0 to 1.6. On the face of these statistics, infection maintained its position as the leading cause of death.

TABLE IV. MAJOR CAUSES OF MATERNAL DEATH IN BROOKLYN, N. Y.

	1937	1938	1939	1940	1941	TOTAL
Total No. Deaths	164	135	110	111	79	599
Infection	30	27	30	22	12	121
Toxemia	26	18	12	17	8	81
Hemorrhage	21	24	13	11	12	81
No. of Births (in thousands)	40.3	40.3	40.3	42.1	48.3	

The downward trend was well maintained for all three principal causes of mortality. However, not all the causes were reported on the certificates of death; neither infection nor toxemia was forgotten or ignored, but very often hemorrhage was not mentioned or, if reported, was considered only as an associated cause by the vital statisticians and so not tabulated. In 1940, for example, the number of deaths from hemorrhage appeared to be but 11, but there were 17 additional deaths in which hemorrhage was coded as a secondary cause. Statistical precedence had been given to infection in 4 cases, toxemia 2 cases, cesarean section 3 cases, embolism 1 case and abortion 3 cases. And in the lists of deaths associated with pregnancy but assigned to nonpuerperal causes, 4 more cases of hemorrhage were found. They are of interest.

1. Streptococcal pneumonia associated with placenta previa which caused repeated and profuse hemorrhage. Delivery was effected by Pinard maneuver.

2. Hemorrhage and shock following induced incomplete abortion associated with rheumatic heart disease.

3, 4. Two women with syphilis who died of hemorrhage and shock, one after post-partum hemorrhage, and the other after rupture of uterus.

In every one of these 17 cases, hemorrhage was profuse, and in many the actual cause of death.

When certificates of death were compared with actual case reports submitted to the Committee on Maternal Welfare of the Medical Society of the County of Kings, it was found that neither infection nor toxemia had failed of report. Hemorrhage, however, had often been omitted, and even when reported as an important contributory factor, had disappeared under joint cause rules. If 37 deaths directly due to hemorrhage and shock, but assigned otherwise, are added to the hemorrhage factor, and proper corrections are made elsewhere, hemorrhage appears as the most frequent cause of maternal death.

TABLE V. MAJOR CAUSES OF MATERNAL DEATH
(REVISED)

	1937	1938	1939	1940	1941	TOTAL
Infection	27	27	30	18	10	112
Toxemia	26	18	12	10	8	74
Hemorrhage	29	27	14	28	20	118

If the figures are further revised so as to include 9 additional cases, in which hemorrhage was known to be profuse or repeated, yet not the actual cause of death, the importance of hemorrhage and its failure to yield to preventive measures becomes even more apparent. And, if it is accepted that the principal purpose of tabulating the causes of maternal death is to plan and accomplish their prevention, then the deaths assigned to accidents of childbirth might well be taken into account, as they are largely associated with, or directly due to, the trauma of delivery. Comparisons with years before 1940 are very difficult, but every effort has been made to make corrections in accordance with the 1940 revision of the International List of Causes of Death. If these deaths are included, after deducting those which were directly due to anesthesia, revision of the mortality trends easily shows hemorrhage as the principal cause of maternal death. (Table VI and Fig. 1.)

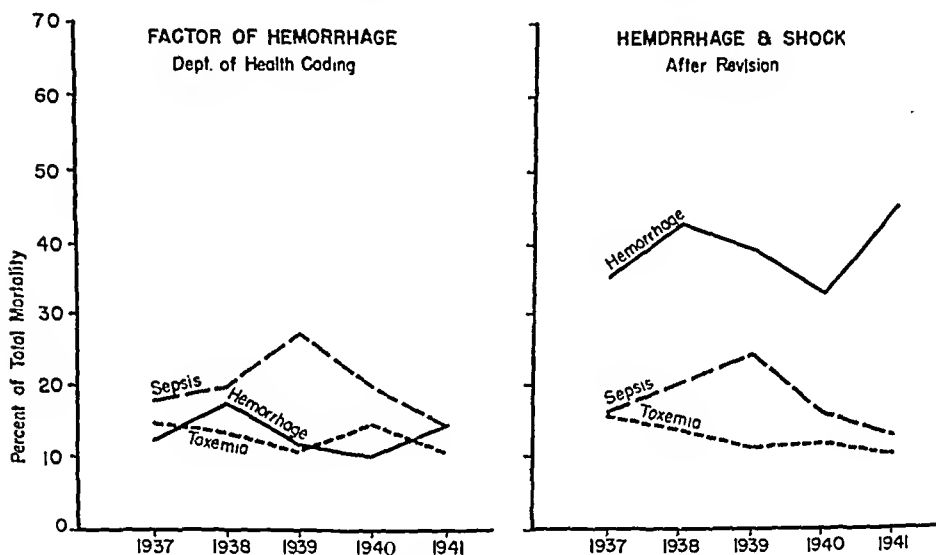


Fig. 1.

TABLE VI. MAJOR CAUSES OF MATERNAL DEATH
(FURTHER REVISION)

	1937	1938	1939	1940	1941	TOTAL
Infection	26	27	27	18	10	108
Toxemia	26	18	12	10	8	74
Hemorrhage	31	29	16	28	23	127
Acc't. Childbirth	29	29	27	8	13	106
Excluding Anesth.	60	58	43	36	36	233

In Brooklyn, hemorrhage is the most frequent cause of puerperal death, and so the most important. Certainly it is not expected that it will prove so in every locality, but it will in many. In Connecticut, for example, with 61 puerperal deaths in 1939 and its low rate of 2.6 per 1,000 live births, hemorrhage was responsible for the largest number. And in the City of Buffalo from 1935 to 1940, 20 per cent of the deaths were assigned to hemorrhage and 23 per cent to sepsis, yet this sepsis rate was greatly influenced by operative delivery, particularly cesarean section. The third largest group was not toxemia, but accidents of

pregnancy and labor, with a high incidence of pulmonary embolism in operative deliveries.

Through the courtesy of the Director of the Bureau of the Census⁹ it has been possible to discover the number of cases in which puerperal hemorrhage and puerperal septicemia were reported as secondary causes, and the number of deaths from these causes which were associated with other puerperal conditions. These figures have not as yet been published. In 1940, a total of 2,207 cases were assigned to infections during childbirth and the puerperium, and 1,037 to hemorrhage of childbirth and the puerperium. There were, however, 363 additional cases in which hemorrhage had been reported as a joint cause but which were tabulated otherwise, 226 of them were assigned to septicemia. And no less than 545 cases of embolism and sudden death which occurred during or after delivery were assigned to infection as well. To other accidents and specified conditions of childbirth, a title which includes laceration, rupture or other trauma of pelvic organs and tissue, and other conditions causing difficult delivery, 550 cases were assigned. There were, however, 1,385 cases in which these conditions had been reported; 456 were assigned to infection and 379 to hemorrhage. It is probable that if case reports were available for comparison with certificates of death, as they are in Brooklyn, the true frequency of hemorrhage would be discovered (Table VIII).

TABLE VIII. HEMORRHAGE AND INFECTION, U. S., 1940

Assigned to infection	2,207
to hemorrhage	1,037
to accidents of labor	550
to embolism and sudden death	545
Hemorrhage assigned otherwise (226 to infection)	363
Total Accidents of Labor	1,385
Assigned to infection	456
to hemorrhage	379
to accidents of labor	550

Comment

Hemorrhage has always been one of the major causes of obstetric death, yet it may be the most frequent cause, and at present it is the most important. Plass¹⁰ believes that "The reduction of the death rate from infection and toxemia by increased efficiency in prevention and treatment threatens to make hemorrhage and shock the leading cause of obstetric fatalities if they do not already occupy that unenviable position."

No doubt there is progressive increase in blood volume during pregnancy and particularly in the later months. And it is true that the parturient woman is often able to survive the loss of a large amount of blood. Yet it is exactly this impression or experience that is responsible for frequent failure to carry out thoughtful prophylaxis or to make adequate preparations for blood replacement. Hemorrhage cannot always be prevented, but the results of blood loss are largely controllable.

In abortion and ectopic pregnancy, hemorrhage is usually repeated before it becomes considerable. Vaginal examinations and long periods of trial of oxytocics are often followed by slow or inept removal of re-

tained tissue with free bleeding. It is common for patients to return to bed with evidence of severe blood loss in the operating room.

In Brooklyn, the placenta previa mortality has been largely due to procrastination. In no case did initial hemorrhage cause death. In 18 out of 26 cases, repeated hemorrhage occurred before any treatment was instituted, a week or more elapsing in 12 cases.

Thoughtless management of the third stage of labor invites postpartum hemorrhage. Blood loss from an episiotomy wound is rarely negligible, and may be considerable, while repair is going on under unduly prolonged anesthesia. The anesthesia itself, if ether or chloroform, may interfere with normal contraction and retraction after delivery of the placenta. Abdominal delivery, too, may be associated with unexpected and serious hemorrhage, particularly the classical operation.

Whether shock can be caused by uncomplicated hemorrhage, according to Blalock,¹¹ or cannot, according to Moon,¹² is of no importance in practical obstetrics, for it is certain that hemorrhage is a contributory factor of the utmost importance. Protracted labor with its wounds and pain, its fatigue and discouragement, its anxiety and fear and other emotional disturbances is the battlefield of obstetrics, and its casualties are not very different from those of war. Continuous and rapid dehydration by sweating and vomiting, or failure to replace lost body fluids must surely result in decreased blood volume, increased blood viscosity and capillary stasis. Even comparatively slight bleeding may be followed by death, and it is clear that operative pelvic delivery, with or without serious hemorrhage, is in no way comparable to carefully planned abdominal surgery.

Anesthesia makes a significant contribution. Not infrequently, administration of any anesthetic will bring about circulatory decompensation in those in whom shock is impending, but who appear to be in good condition. Ether and chloroform tend to increase blood loss. Satisfactory analgesia of nitrous oxide is associated with steadily increasing anoxia. Spinal anesthesia, if it has not affected the respiratory mechanism, invites shock by causing vasodilatation. Even analgesics in slow labors, which tend to increase the incidence of operative delivery, merit consideration. Chloral and barbiturates in large doses will increase capillary permeability.¹³ Even morphine tends to cause the anoxia which is so important in the causation of shock. And acidosis will follow well-developed anoxia. Local anesthesia, obviously, will have less general effect than any inhalation anesthetic.

It is not my purpose to examine all the conditions and circumstances which contribute to obstetric hemorrhage, nor to propose a detailed preventive program. Knowledge of methods of prevention is fundamental, and successful management of serious hemorrhage depends largely upon the skill of the obstetrician and timely replacement of lost blood. Hemorrhage cannot always be anticipated, but it is possible to be prepared for it. The implications are clear.

Circulatory efficiency can be maintained only by restoration of blood volume. Surely every physician knows that lost blood must be replaced by blood or a satisfactory substitute, yet, in practice undue confidence is had in almost everything else, and blood and plasma are by no means as widely used as they should be. It is obvious that the best method of treatment of shock involves its early recognition, but not every physician knows that even slight decline in the systolic pressure

is of great significance, and that low blood pressure is not an early symptom. Nor does every physician know that crystalloid solutions are ineffective if blood loss has been serious; that often only large amounts of blood will save life; and that preparations for transfusion from voluntary donors involve valuable loss of time; nor is everyone aware that infusion of plasma may be accelerated by the syringe, when time presses, or that the sternum may be used for administration of blood and plasma, by drip or syringe, when veins are collapsed.

Since citrated blood, because of its availability and ease of administration meets all the requirements of the obstetrician, blood banks are ideal, yet even they are not certain sources of supply even in the largest hospitals. A plasma bank is practical for even the smallest hospital, while a blood bank is not. And plasma, which any hospital may store near its delivery room, is commercially available, yet not every lying-in institution is aware that it must include blood or blood substitutes in its resources. Women cannot be expected to make this inquiry themselves. Perhaps, as a result of the war, a plasma conscious public will contribute blood to avert the casualties of obstetrics, through cooperation of the same agencies which are carrying on this work so well now.

In Brooklyn, hemorrhage is the outstanding controllable factor in puerperal mortality. Far more common everywhere than indicated by its statistical frequency, it has not yielded to preventive measures which can be clearly outlined. At present, hemorrhage is the most important cause of maternal death.

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THE INFLUENCE OF PREGNANCY ON THE LOCATION OF THE CENTER OF GRAVITY, POSTURAL STABILITY, AND BODY ALIGNMENT*

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ONE of the most rigorous demands made upon the human postural mechanism is that of pregnancy. For a period of 280 days the woman carries a steadily increasing load which at term averages, in totum, including uterus and ovum, 4 to 6 kilos (pounds 10-14). Mechanically, this load could scarcely be placed more disadvantageously. The low anterior position of the added weight limits joint adjustments and enhances the normal forwardly unbalancing gravitational stresses. Excessive postural realignments must be necessary to retain the center of gravity within the secure middle third of the supporting base. Further difficulties arise with the relaxation of ligaments and a loosening of the pelvic joints which have been shown to appear as early as the fourth month of pregnancy (Abramson et al., 1934,¹ Thoms, 1936).¹¹ It has seemed reasonable to presume that the low back pains which frequently accompany pregnancy, or develop as a sequel to it, might have an etiology, based in part, upon these disturbances in body mechanics.

Aside from studies made on weight changes and alterations in the pelvic joints few, if any, consecutive observations have been reported of the readjustments in body parts as they accrue in pregnancy and regress during the puerperium. Having available a cooperative subject trained in the laboratory procedures required, it seemed worth while to record the postural adjustments of the gravida by means of serial biplane photographs synchronized with center of gravity observations. The following paper presents the results of the study of the influence of pregnancy on the location of the center of gravity, postural stability, and body alignment.

Methods

The apparatus and procedure were essentially the same as that described by Hellebrandt and Kelso (1942).⁶ The subject (R. T. C.), a young secundigravida, aged 31, reported to the laboratory for nine observations, distributed in two-week intervals at the beginning and end of term. The following data were obtained for each of the experiments: weight in kilos and pounds, height of the center of gravity and the total height in recumbency, and kymogram records of postural stability during two minutes of comfortable standing with biplane profile and back view photographs taken every 15 seconds. Thus each experiment

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yielded a total of 18 photographs synchronized with center of gravity observations.

A planimetric average of the shifting gravity center for the single stance periods was calculated and projected into the footprints. Experimentally determined gravity lines were then erected into each photograph.

The initial record was made during the third month of pregnancy. The next two followed at the end of the first and at the beginning of the second trimester. No further observations were possible until the third trimester when biweekly experiments were resumed, the last one being performed ten days before delivery. A final observation was made six weeks after parturition.

Results and Their Interpretations.

Table I presents a summary of the data recorded. Eccentricity is the per cent deviation of the experimentally determined center of gravity from the diameter passing through the geometric center of the supporting base in each of the two vertical orientation planes (Hellebrandt et al., 1937).⁷

1. *Height of the gravity center.*—The per cent height of the weight center is the ratio of the gravity height from the soles of the feet to the total recumbent height of the subject as measured by means of the gravity board developed in this laboratory (Hellebrandt et al., 1938).⁸ The range of the gravity height ratio for women is 53.00 per cent to 59.00 per cent. That of our subject at the end of the first trimester was 54.68 per cent, placing her within the lower quartile of the group of 464 normal young adult women studied by Hellebrandt et al. (1938).⁸ At the end of term the ratio had risen to 55.99 per cent to the score level of the upper quartile, representing a 2.40 per cent increase in the height of the gravitational center. This progressive increase in gravity height throughout pregnancy may be contrasted to the work reported by Okuyama (1933)¹⁰ who studied the gravity height changes in fourteen subjects at various times before pregnancy, and once during puerperium. He found no consistent rise in the weight center height and in some cases there was an ante-partum fall in the gravity center. The discrepancy may be explained by the difference in the methods used. Okuyama employed a device necessitating the raising of one end of the gravity board through a known angle. This procedure might well cause a displacement of the viscera and fetus and thus, explain the variation of his records as compared to those obtained on the simple gravity board used in our experiment, where the position of the subject was held constant.

2. *Eccentricity in the sagittal plane.*—The mean location of the center of gravity for each observation was projected into a single footprint of the subject (Fig. 1). The hollow circles show the proximity of the average location of the gravity center to the geometric center of the base during the first trimester when the total weight was approximately 65 kilos, and the eccentricity -2.00 per cent. The semi-solid circles indicate the posteriorly displaced gravitational center during the third trimester when the weight ranged from 73.75 kilos to 75.70 kilos. During this period the eccentricity varied from -5.10 per cent to -17.86 per cent. The greatest eccentricity was concomitant with the greatest weight increase (Table I).

TABLE I. SUMMARY OF DATA OBTAINED IN A STUDY OF THE INFLUENCE OF PREGNANCY ON BODY MECHANICS—SUBJ. R. T. C.

EXPERIMENT	ECCENTRICITY		WEIGHT KG.	HEIGHT OF CENTER OF GRAVITY PER CENT
	AP PER CENT	LAT PER CENT		
1	-2.65	-1.82	65.00	54.68
2	-2.01	-0.88	65.20	54.51
3	0.00	-3.19	67.10	54.63
3rd Trimester				
4	-5.10	-9.01	73.75	54.93
5	-11.12	-1.83	73.80	54.99
6	-5.58	-4.75	74.25	55.22
7	-17.86	-9.07	75.70	55.52
8	-12.05	-6.50	75.15	55.99
Post Partum				
9	+2.02	-5.11	65.00	54.56

+In front of the geometric center of the total base.

-In back or to the left of the geometric center of the total base.

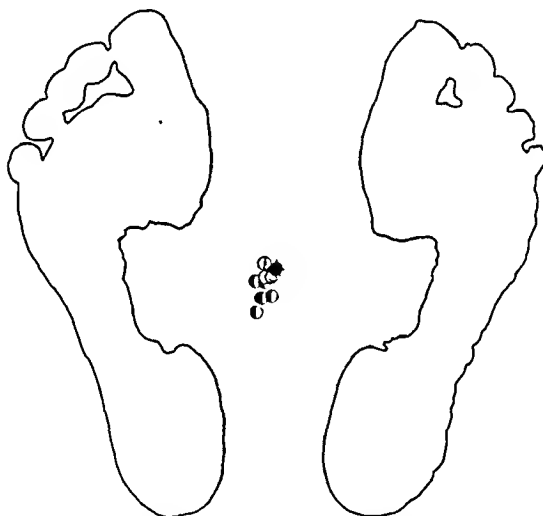


Fig. 1.—Footprint showing the average location of the vertical projection of the center of gravity of R.T.C., for each two-minute observation made during pregnancy and puerperium.

The apparent direct relationship between weight increase and rise in center of gravity height with the backward deviations of the per cent eccentricity in the sagittal plane may be expressed numerically. The anteroposterior eccentricity was correlated by the rank difference method with the weight increase, giving a correlation coefficient of 0.83. Thus with an augmentation in the subject's weight, the vertical projection of the center of gravity moves closer to the ankle. Coincidental with the weight increase there is a rise in the gravity center in the horizontal plane. This, then, also shows a high correlation with the backward displacement of the center of weight and $r = 0.93$.

The puerperal resumption of the anterior position of the average gravity center is represented by the barred circle. The vertical projection of the center of gravity is approximately in its initial position close to the geometric center of the base with an eccentricity of only +2.00 per cent. The weight is again 65 kilos and the center of gravity height

lowered to 54.56 per cent as compared with the 54.68 per cent in the beginning of pregnancy. Thus, there is an almost exact return to original values of three factors: body weight, height of the center of gravity and stance eccentricity.

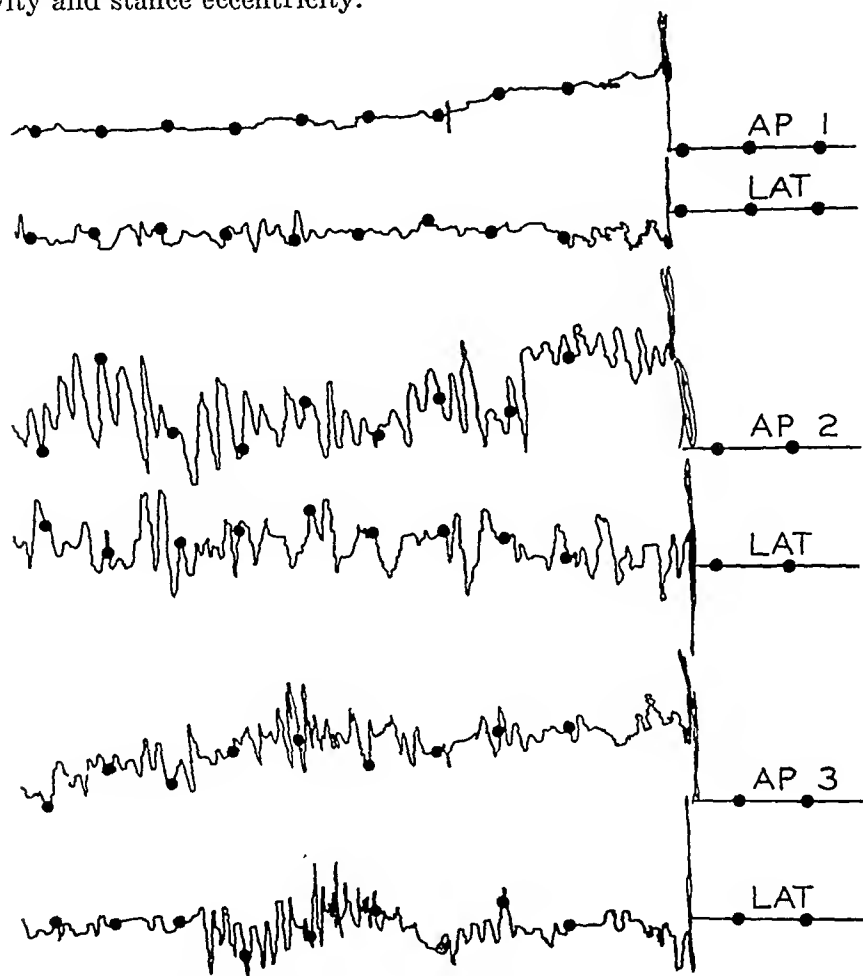


Fig. 2.—Kymograms of the shifting gravitational center of subject R.T.C. 1. First trimester; 2. Ten days ante partum; 3. Six weeks post partum.

3. *Location of the average center of gravity in the transverse plane.*—The planimetric averages of the shifts in the center of weight in the coronal plane do not vary more than 10 per cent. The subject stood with the weight slightly to the left of the geometric center of the base. This asymmetry has been demonstrated as occurring in approximately 80 per cent of all cases observed in this laboratory (Hellebrandt and co-workers, 1939-1942.^{3, 4} Apparently the added weight of pregnancy is so balanced that this fundamental asymmetrical stance pattern remains undisturbed in spite of the fact that the gravity center is displaced in the anteroposterior plane.

4. *Postural stability.*—A gross inspection of the kymograms of the shifting gravity center shows an increase in body sway throughout the period of pregnancy. One would expect such accruing instability to be associated with a rise in the height of the center of gravity and development of the fetal load. However, much of this sway was still present

post partum. Fig. 2 shows the anteroposterior and lateral records of the shifting center of weight. Apparently the initial degree of stability had not yet been reattained at the end of the puerperium. It is logical to assume, however, that, with the mechanical difficulties offered by the load and the loosening of the pelvic joints, the increase in sway during pregnancy is due to a decrease in postural stability which has a combined physical and organic basis. As it may involve a stretching of ligaments, postural stability is, perhaps, not as readily restored to pre-gravida conditions as are the other mechanical phenomena.

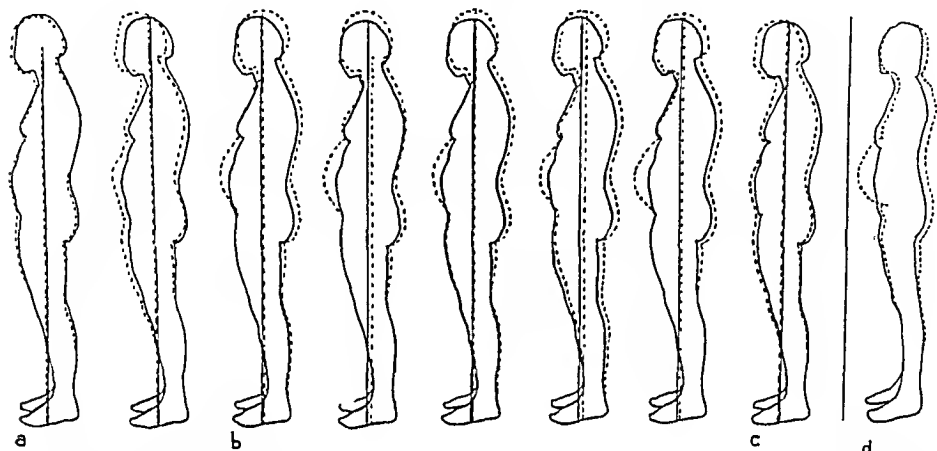


Fig. 3.—Tracings of superimposed photographs demonstrating the postural changes accompanying pregnancy.

"a," "b," and "c." Subject R.T.C. Successive observations (No. 2 through No. 9) are compared in turn (dotted line) with the photograph from experiment No. 1 (solid line) taken early in pregnancy.

"a." First trimestral series

"b." Third trimestral series

"c." Six weeks post partum

"d." Subject H.N. A photograph taken 24 hours ante partum (dotted line) is superimposed upon one of the same subject made 20 days after parturition.

5. *Body alignment.*—Changes in body contour and distribution of the segmented parts are demonstrated in Fig. 3. The solidly outlined figure represents the distribution of the body parts about the vertical projection of the center of gravity during the third month of pregnancy, at the time the first experiment was performed. Each successive observation is superimposed in turn upon this figure ("a" through "e") showing the gradual changes occurring throughout the ante-partum period with a rather striking return in the puerperium to the initial stance position. For comparison, observations made on a second subject (H. N.) of a much slighter build are included ("d").

The photographs of R. T. C. chosen for this study were those that most nearly approached the average location of the center of gravity in the sagittal plane during each period of observation.

Figs. "a" represent the stance at the end of the first trimester before any outstanding changes due to pregnancy have appeared. The head is forward. The upper back is well rounded and the knees relaxed. Figs. "b" are illustrations of the biweekly observations of the third trimester. A marked alteration in body contour may be noted. The gravity line moves backward. The head is raised, and the knees are stabilized. In Fig. "c," taken at the end of puerperium, the head has fallen forward, the back again is rounded, the knees relaxed and the gravity line resumes the original anterior position. This illustrates

the constancy of the stance of a normal individual (Hellebrandt⁴ and Fries, 1942).⁵

Parallel changes seem to occur in subject H. N. ("d"). The solid line is the outline of a photograph taken 20 days post partum. The dotted line shows the posture and appearance of the subject 24 hours prior to delivery.

In both subjects H. N. and R. T. C. there appears to be an unexpectedly slight change in the lumbar region of the spine. The curves in both cases appear almost parallel. In R. T. C. there is a suggestion of a sharpened lumbar curve and the apex of the angle may be slightly higher during the last months of pregnancy, suggesting some pelvic rotation. The data seem to indicate that the major counterbalancing adjustments are made by elevating the head, extending the cervical spine, stabilizing the knee joint, and leaning backward from the ankle.

Discussion

The results corroborate to a certain extent the accepted concept of postural changes in pregnancy (DeLee and Greenhill, 1943).² The upper back does appear to be straightened. However, analysis of the pictures seems to demonstrate little actual change in the dorsal spine *per se*. Instead, the straightening occurs primarily in the cervical region. Similarly the "exaggerated lumbar curve" commonly thought to occur, is not prominent in our subjects. One might surmise from these two cases that in certain individuals the upper body is retro-extended as a whole to counterbalance the increased forward load. Kerr and Lagen (1936)³ state that in pregnancy the head falls forward and the knees are bent and relaxed. Our experience seems to indicate that the adjustments are made entirely in the opposite direction, with a raised head and a stiffening of the knee joint.

It appears evident that with an increase in the anteriorly placed load the subject compensates by leaning backward beyond her normal gravitational center. This apparent "overcompensation" to a poorly placed weight which must be carried for a long period of time, can be contrasted to the comparatively slight disturbing influence of a much heavier load carried on the back. In this latter position, the added mass to the back acts as a counterweight to aid the subject in opposing the forwardly unbalancing gravitational forces. Furthermore, adjustments to a dorsal load are made by anterior body lean, with the degree of motion limited by the powerful antigravity muscles. The subject carrying a weight on the back can readily achieve an equitable balance between the added load and collapsing gravitational stresses and the center of weight remains essentially undisturbed (Hellebrandt, Fries and Larsen, 1942).⁵ In contrast, during pregnancy the added weight augments the normal forwardly unbalancing effects of gravity, and the controlling antagonistic muscular action is through the comparatively weak flexor groups. Thus, the position of the load and the resulting direction of the counterbalancing reactions make fine equilibratory ad-

justments difficult. However, the machine more than compensates. It widens the margin of safety anteriorly, and thus protects against an acute unbalancing force which might lead to a forward fall, endangering the fetus.

Summary

1. The anteriorly unbalancing load of pregnancy causes a temporary overcompensation which displaces, backward, the average location of the vertical projection of the center of gravity in the sagittal plane.

2. Pregnancy appears to be associated with no alteration in the subject's normal sinistral asymmetry of stance.

3. The multijointed segmented body counterbalances the disequilibrating effects of pregnancy by elevation of the head, hyperextension of the cervical spine and extension of the knee and ankle joints. Relatively slight visible adjustments occur in the lumbar spine.

4. There is an apparent significant decrease in postural stability which persists throughout the puerperium.

5. Since the alignment at the end of puerperium is an almost exact duplication of that assumed in the early months of pregnancy, the gravida has successfully resisted the chronic disrupting force without any significantly permanent change in the postural mechanism.

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THE SIGNIFICANCE OF THE ERYTHROCYTE SEDIMENTATION RATE IN PELVIC PATHOLOGY*

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THE erythrocyte sedimentation rate has been generally accepted as an aid in the diagnosis of infections and in the interpretation of normal and destructive processes. However, reports of the results of this simple test have been very conflicting. Two possible factors may be responsible; first, the nonspecificity of the test and secondly, the lack of uniformity in technique. A rapid sedimentation rate may not necessarily be due to a lipoma of the arm found coincidentally. Similarly, a limited physical examination invalidates the interpretation of the sedimentation rate. The test is not specific. The lack of uniformity in technique is due mainly to our ignorance of the mechanism underlying this phenomenon and adds further to the confusion.

From experimental^{2, 21} and clinical^{4, 18} observation, it has been found that the factors responsible for the sedimentation of erythrocytes are contained in the plasma. Cutler has shown that when the cells of slowly sedimenting blood were transferred to the plasma of rapidly sedimenting blood, they settled rapidly; whereas, when the cells of rapidly sedimenting blood were transferred to the plasma of slowly sedimenting blood, they settled slowly. The addition of lecithin, sodium oleate, bile salts or formaldehyde to rapidly settling blood, inhibited sedimentation; while the cells so treated when resuspended in "fast" plasma, again settled rapidly. The addition of acacia, agar, casein or gelatin to slowly settling blood increased the sedimentation.

Methods

There are three accepted methods of performing this test: (1) the Linzenmeyer method which determines the time required for a column of red blood cells to settle 18 mm.; (2) the Westergren method of recording the column of red cells after 15 to 30 minutes; one, two, six and twenty-four hours of settling; and (3) the Cutler graph method.³ Renwa¹⁵ stated that the Westergren method is most reliable because of the frequent intervals of recording. It would seem that the graph method would be even more reliable with readings recorded every five minutes for one-half hour, since the important phase of the sedimentation occurs in the first half-hour. The graph method, therefore, was used throughout this study.

Using a graph, the sedimentation of the erythrocytes in a 50 mm. column of citrated blood is interpreted thus: "A maximum settling in five minutes of 1 mm. or less, with the 1 mm. rate not repeated more

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than twice during the half-hour, is normal. Everything else is abnormal and therefore pathologic. Generally speaking, a maximum rate in 5 minutes of 1 mm. with the 1 mm. repeated three or more times during the half-hour, or rates between 1 and 4 mm., indicates disease of slight intensity; rates of 4 to 9 mm. indicate moderate intensity, and rates of 10 mm. or more, marked intensity." To facilitate recording, the normal graph is specified as reaction 0, that of slight intensity as reaction I, that of moderate intensity reaction II, and the curve of marked intensity as reaction III.

The three phases of sedimentation, i.e., formation of rouleaux, actual sedimentation of the aggregates and the packing of the red cells, become evident. An interpretation based on the maximum fall in millimeters in five seconds, is definitely more sensitive than an interpretation based on the fall in millimeters in one hour or on the time necessary for the red cells to fall eighteen millimeters since the latter two usually include all three phases.

A graph taken in case M. N. of epidermoid carcinoma, grade 3 of the cervix, League of Nation's classification stage 2, showed that the graph interpreted the line as reaction I, while the total fall of 10 mm. in one hour was on the borderline between normal and abnormal sedimentation.

Correction for anemia is misleading, as shown by Cutler, Park and Hess, Diggs and Bibbs,⁵ and Whitting and Miller.²¹ Anemia plays a part in the third phase and prolongs the second phase only by delaying packing. It is the pathologic condition with subsequent anemia that produces the rapid sedimentation, not the anemia per se. Both Cutler and Diggs reported normal sedimentation in severe anemia associated with sickle cell anemia. In this series of cases, one patient with recurrent anaplastic carcinoma of the ovaries in the terminal stage, had a hematocrit of 15 and a normal sedimentation rate. With the graph method, the packing phase does not affect the reading.

The actual conditions for the performance of the test in this study were set down as follows: (A) Blood should be taken either before a meal or at least two hours after eating. Recent investigation however⁷ does not substantiate the report of any increase in erythrocyte sedimentation rate after food. (B) The test must be performed within two hours after the blood is taken because there is frequently a decrease in the sedimentation rate after the blood has stood for 4 to 6 hours. (C) The Cutler sedimentation tube must be suspended in air to insure a vertical position as an inclination of 2.3 degrees gave a 30 per cent error in a 100 mm. length tube.²² This was readily accomplished by the use of an ordinary rubber stopper with a loop of thread passed through its center. (D) 0.5 c.c. of 3.8 per cent sodium citrate was used for every 5 c.c. of blood. The citrated blood was stored in a refrigerator at a temperature slightly above freezing. Any blood which showed evidence of clotting or hemolysis was discarded as unsuitable.

Results

Two hundred and nine tests were performed on 205 patients. Of these, one hundred and thirty-nine had benign lesions and sixty-six had malignant tumors. The benign lesions included infections, cysts, tumors and pregnancies. The malignant tumors included sixty-five cases of carcinoma of the genital tract and one case of myosarcoma of

the uterus. Repeated readings of seventy samples of blood were taken after six, and after twenty-four hours of standing in vitro.

Benign Pelvic Lesions

Bartholin cysts, relaxed perineal floor, cervicitis, malposition of the uterus and endometrial hyperplasia do not cause a rapid sedimentation rate. Bartholin abscess, lymphogranuloma venereum and ulcer of the cervix after cauterization cause a rapid sedimentation rate. Sedimentation rate does not help in differentiating a benign from a malignant ulcer of the cervix.

There were fifty-one cases of uterine fibroid. Forty-one or 80 per cent gave an erythrocyte sedimentation rate of reaction 0 or I_2 , i.e., reaction I with a maximum rate of 2 mm. per five minutes. Ten cases gave a reaction over I_2 . These ten patients were found either to have other pathologic conditions associated with the fibroma to account for the rapid rate, or developed serious complications postoperatively. In two cases, the fibroma was associated with pregnancy between the third and fourth months. One patient showed evidence of an old infected incomplete abortion. Another had tubercular appendicitis in addition to the uterine fibroma. Two patients developed bronchopneumonia and one a *B. coli* urinary infection. Two developed thrombosis and in one of these cases death followed a pulmonary embolus. In one patient there was nothing to account for the rapid sedimentation except that she had received a transfusion of 500 c.c. of whole blood the day before the test was performed. The relationship of rapid erythrocyte sedimentation to the subsequent development of complications is not clear.

Eighty per cent of all the patients with fibroma of the uterus not coincident with other pathologic conditions showed a normal or slightly rapid sedimentation rate. Those in whom the result was abnormal to the extent of reaction I_2 , gave evidence of hemorrhage, necrosis and calcification in the fibroid, although such degeneration did not invariably increase the sedimentation rate. Mathieu¹³ in his thirty-nine cases of uterine fibroma made the statement that a bleeding submucous fibroma causes rapid erythrocyte sedimentation. I could not confirm this finding. It may be questioned whether it was the degeneration and infection in the submucous fibroid that caused the increased rate, or a recent transfusion for combating the severe anemia was responsible. It can be stated that a normal sedimentation rate, or one of reaction I_2 , or less, is a safe indication for surgery in fibroma of the uterus. A patient showing an increased sedimentation rate of I_2 , or higher, warrants further study to determine the probable presence of some other pathologic or physiologic condition.

There were twenty-five cases of pregnancies in this series. Six were in the last trimester, five in the second and fourteen in the first. The sedimentation rate was found to be increased in all the patients in the second and third trimesters. These results agreed with those obtained from larger series of pregnant women.^{1, 20} The rate was found to be variable in the first trimester. It was increased in two of three non-infected intrauterine pregnancies in the third month, in two of four patients in the second month. Two patients with infected incomplete abortion showed a rapid sedimentation rate. There were five cases of ectopic pregnancy of less than two months' duration. Increased sedimentation rate occurred in two patients who had massive hemoperi-

toneum. However, in two with some free peritoneal blood, and one without bleeding, the rate was normal. Hemoperitoneum therefore, unless massive, does not cause an abnormal sedimentation rate. A rapid rate in a suspected ectopic pregnancy, unless there is clinical evidence of hemoperitoneum, is against such a diagnosis and urges consideration of an inflammatory process.

The use of the erythrocyte rate in the differential diagnosis of salpingitis and appendicitis has been repeatedly reported.¹⁰⁻¹⁰ There are conflicting reports regarding the rate in acute appendicitis, although most writers agree that salpingitis gives a much more rapid rate than appendicitis. Lesser and Goldberger reported a normal rate while Lintgen and Fry found an abnormal rate in 52 per cent of the patients with appendicitis without rupture, including catarrhal, suppurative and gangrenous appendicitis. Lesser and Goldberger used the Westergren technique while Lintgen and Fry used the graph method. The sedimentation rate in the two cases of purulent appendicitis included in this study gave reaction I, while that of a ruptured appendix with pelvic abscess reaction II, and all appendicitides considered as "chronic" had a normal sedimentation rate. There were six patients with inflammation of the adnexa. Three were diagnosed as fibroma preoperatively, and laparotomy revealed a tuboovarian abscess and chronic salpingitis with sterile culture. The sedimentation rates ranged from reaction I to II. The other three were cases of acute salpingitis with sedimentation rates ranging from reaction II to III.

An explanation for the difference between the acceleration of the sedimentation rate in appendicitis and that in salpingitis has been suggested by Smith. He attributed it to the difference in the time of onset of symptoms. The Fallopian tubes, being more distensible, do not cause symptoms as readily as does the appendix. Therefore, inflammation has been established in the tubes for some time before causing symptoms, thus accounting for the higher sedimentation rate in salpingitis.

Among the ten benign ovarian tumors, which included parovarian cysts, pseudomucinous and serous cystadenoma and thecoma, the sedimentation rate was essentially normal except in those cases with complications. The five cases associated with rapid sedimentation rates were as follows: one had twisted pedicle, two were in the second trimester of pregnancy, one was associated with carcinoma of the breast, and the last case showed extensive necrosis and inflammation in the ovarian tumor.

Malignant Pelvic Tumors

There were three cases of squamous carcinoma of the vulva, grades 1 and 2. Two patients, showing evidence of groin metastases on admission, had been surgically treated. The third was treated by local caustic before admission and presented clinically an early lesion 1 cm. in diameter; microscopically the inguinal nodes presented no pathology. The sedimentation rate in the case of the last patient was normal while those of the first two gave reactions I and II respectively.

There were thirty-eight cases of epidermoid carcinoma of the cervix, five grade 3 and thirty-three grade 2, 8 per cent and 92 per cent respectively. Of these four were clinically classified as League of Nations stage 1, eleven stage 2, twelve stage 3, and three stage 4. Eight had been treated previously, therefore, it was not possible to classify them. All

TABLE I. CARCINOMA OF THE CERVIX

CLASSIFICATION	REACTION			
	I	II	III	NORMAL
L. of N. stage 1 (4 cases)	75%	25%	0	0
L. of N. stage 2 (11 cases)	91%	9%	0	0
L. of N. stage 3 (12 cases)	50%	50%	0	0
L. of N. stage 4 (8 cases)	33%	67%	0	0
Those treated elsewhere				
"No evidence of disease" (3 cases)	100%	0	0	0
"With evidence of disease" (5 cases)	20%	40%	40%	0

showed abnormal sedimentation rates varying from reaction I to III. The degree of rapidity depended partly on the extent of the disease, but more on the amount of infection present (Table I). This was brought out by the fact that reaction III occurred only after irradiation and one patient with this reaction had a left adnexal abscess as well. It is important to note that there were three patients, who had no evidence of the disease after being treated elsewhere, but still maintained an abnormal sedimentation rate.

There were thirteen cases of malignant lesions of the fundus uteri. Twelve were adenocarcinoma and one was myosarcoma. Eighteen per cent of the patients who applied for treatment were in the operable stage. The sedimentation rate was found to be increased in all cases.

Jacoby and Spottoff⁹ stated that 48 per cent of their ninety-one cases of uterine cancer had normal sedimentation rates. Seventy-one were cervical and twenty fundal in origin. This is in distinct contrast to the findings in this series in which only 3 per cent of the sixty-six patients with malignant lesions gave a normal sedimentation rate. However, the method used by these investigators was not given and 15 mm. was taken as their limit between normal and abnormal sedimentation rate. It might be presumed that it was 15 mm. fall of erythrocyte per hour. If the tubes were 100 mm. in length, the results might be comparable to the Cutler's 50 mm. tube, as length of the tube has been shown to affect the rate of fall.³ However, without uniform technique, it is difficult to compare the results.

Among the ovarian neoplasms, seven were malignant. There were four additional patients who had generalized abdominal carcinomatosis with ascites. The primary tumor cannot be definitely determined, either clinically or at post mortem, but most probably it was ovarian. Contrary to what might be expected, even in patients with ascites, the rapidity of the erythrocyte sedimentation rate was not remarkable. It ranged between reactions I and II only. One patient, No. 68462, with recurrent anaplastic carcinoma of the ovaries, with necrosis and hemorrhage, metastasis to the peritoneum with fibrinous peritonitis, paralytic ileus, ascites and pleural effusion, gave a normal sedimentation rate with a hematocrit of only 15. Wise and Durham²³ in their investigation of the sedimentation rate in Hodgkin's disease noted two cases showing normal sedimentation rate in the terminal stage. Gilligan and Erinstein⁸ in attempting to establish the relationship between the sedimentation rate and the fibrinogen content of plasma, mentioned one terminal case with severe liver damage which gave a sedimentation rate and fibrinogen content below the limit of normal. Cutler also observed a normal sedimentation rate in the terminal stage of tuberculosis. It is conceivable that in such patients, the factors most probably responsi-

ble for the rapid rate, the plasma proteins, have been greatly reduced because of the markedly diminished liver function.

On the whole, those patients with ovarian cancer, even with ascites, appeared more comfortable and had very little pain as contrasted with patients in a similar stage of cancer of the cervix. The clinical discomfort of the patient thus parallels the rapidity of the sedimentation rate. The cases of cancer of the cervix with reactions II and III were invariably associated with a great deal of infection. Reichel¹⁴ made the statement that the rate was not the reaction of the cancer, but rather the manifestation of resorption capacity for inflammatory and necrotic products. This emphasizes the importance of controlling infection for the greater comfort of patients with cancer of the cervix in the advanced stage of the disease.

Feldman⁶ reported 95 per cent maintenance of the sedimentation rate, in vitro, throughout twenty-four hours after withdrawal of blood in cases of malignant tumors and Hodgkin's disease in contrast to those with inflammatory processes whose rapid sedimentation rate showed a reduction toward normal after twenty-four hours. He advocated the additional observation of the sedimentation rate at the end of twenty-four hours as a means of differentiating malignant tumors from other conditions giving a rapid rate. In an attempt to corroborate his findings, fifty-one cases with malignant tumors and nineteen cases with inflammatory process, with rapid sedimentation rates, had repeated readings at the end of six, and twenty-four hours. In contrast to Feldman's findings, of the patients with malignant tumors, nineteen out of fifty-one (37 per cent) showed a decrease in the rate of sedimentation; and of the patients with inflammatory processes, only ten out of nineteen (53 per cent) showed a decrease. There is too little difference between the percentages in this series to give any significance to repeated sedimentation tests at the end of twenty-four hours. A possible explanation of the reduction in the rate after standing in vitro may be that irrespective of the cause of lesion, the less extensive it is, the greater the tendency towards a normal sedimentation rate. (Tables II and III.)

TABLE II. REDUCTION IN SEDIMENTATION RATE AT END OF 24 HOURS IN CARCINOMA OF THE CERVIX

L. of N. stage 1	75%
L. of N. stage 2	33%
L. of N. stage 3	16%
L. of N. stage 4	33%

TABLE III. REDUCTION IN SEDIMENTATION RATE AT END OF 24 HOURS IN INFLAMMATORY DISEASES*

Mild inflammatory processes (8 cases)	88%
Severe inflammatory diseases (11 cases)	27%

*Mild inflammatory diseases included lymphogranuloma venereum, salpingitis, etc. Severe inflammatory process included advanced tuberculosis with mixed infection.

After irradiation, the sedimentation rate may be temporarily increased, as observed by Madrazo¹² and Jacoby⁹ and in the few irradiated cases of carcinoma of the cervix included in this series. As a guide to prognosis, after the local lesion is well controlled, Jacoby and Spottoff stated that a normal sedimentation rate gave hope of a "cure" while a persistent rapid rate called for closer observation for recurrences.

Summary

Two hundred and nine erythrocyte sedimentation tests were performed on two hundred and five patients as a diagnostic aid in pelvic pathology. Of the two hundred and five patients, one hundred and thirty-nine had benign lesions and sixty-six had malignant tumors. Among the benign lesions, pregnancy and infection increased the sedimentation rate. Ninety-seven per cent of malignant tumors showed a rapid sedimentation rate. Persistence of the rapidity of the sedimentation rate at the end of twenty-four hours in vitro does not differentiate malignant tumors from inflammatory processes.

The test is a definite aid in differential diagnosis in pelvic pathology. As in nonspecific laboratory procedures, the result must be interpreted in conjunction with clinical history and findings. It is also important to have uniform technique before a comparison of results from various clinics can be made.

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PREGNANCY AND THE DOUBLE UTERUS

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LACK of fusion of the müllerian ducts, either complete or incomplete, presents to the obstetrician and gynecologist a problem which demands knowledge of the dangers which may result from this anomaly. Since the deformity occurs only once in about 1,500 obstetric, and about once in 2,000 gynecologic cases, it is probable that even the specialist may see but few cases in a lifetime.

Terminology

There is some confusion in naming the different degrees and types of the anomaly. All degrees of lack of fusion of the müllerian ducts exist, from notching of the uterus, as in uterus arcuatus, to two complete sets of genital organs. The uterus may be divided completely, or by a septum, and likewise the cervix and vagina may be partially or completely divided. Hence, the uterus alone, the uterus and vagina together, or the vagina alone may be affected. When the müllerian ducts fail to develop normally as well as fail to fuse, then one uterus or vagina, or both, become rudimentary organs. DeLee¹ lists nine variations as follows:

1. Uterus duplex bicornis cum vagina septa.
2. Uterus septus duplex or uterus bilocularis.
3. Uterus subseptus unicollis.
4. Uterus subseptus unicorporeus.
5. Uterus arcuatus.
6. Septate vagina.
7. Uterus bicornis unilaterale rudimentarius.
8. Uterus with closed accessory horn.
9. Uterus unicornis.

Graves² lists eight types which do not correspond in description or in terminology with the above. In any event, such terms do not immediately present a clear-cut picture and must be accompanied by a detailed description to be comprehensive. Such confusion could be avoided by a simplified classification, as:

1. Uterus arcuatus.
2. Double uterus with a single cervix.
3. Septate uterus with a single or a septate vagina.
4. Double uterus with a double cervix.
5. Uterus with a rudimentary horn or absence of one horn.

In this it will be noted that the terms "septate" and "uterus arcuatus" have been retained since they are in general use. The terms "bicornuate" and "uterus didelphys," frequently used interchangeably in the literature, are confusing and should be discarded. There are, of course, cases not covered by this proposed classification, but a few modifying words would be sufficient to denote variations.

Pregnancy in cases of double uterus is always an interesting phenomenon. The following cases are taken from the records of the New Haven Hospital and represent cases seen over a past ten-year period.

Case 1.—Pregnancy in a septate uterus with a septate vagina.

O. W., a 25-year-old primigravida, whose anomaly "double vagina and double uterus" was diagnosed correctly by her local physician. Difficulty during coitus was easily remedied without operation when the defect was explained to the couple. The patient was referred to the New Haven Hospital obstetric clinic when she became pregnant.

First seen on February 16, 1941, she gave her last menstrual period (L. M. P.) as October 8, 1941. History and physical examination were negative except for a history of severe dysmenorrhea. There was no history of pelvic anomalies in the family. Pelvic examination revealed a septate vagina; left side was somewhat smaller, both sides admitted two fingers without discomfort. Two separate, somewhat infantile, cervixes were demonstrated. The right cervix was softened and was the site of a small cervical polyp. On bimanual examination, it was felt that there were two separate uteri, the one on the left being normal in size, the one on the right being enlarged to the size of a two months' pregnancy, soft and boggy.

Roentgen pelvimetry revealed an essentially adequate pelvis. On February 28, 1942, the patient was admitted, having had cramps and vaginal bleeding for two hours prior to admission. Physical examination revealed the uterus on the right side to be the size of a 4 to 5 months' pregnancy. Fetal heart rate was normal, definite contractions were felt. Pelvic examination showed the bleeding coming from the nonpregnant side. Diagnosis, threatened abortion. The patient was kept under moderate sedation and was given progesterone for the next three days. The fetal heart rate remained good, while the slight vaginal bleeding and uterine cramps continued until March 2, 1942, when a uterine cast was expelled from the left uterus. The pathological report was "decidual cast with acute and chronic inflammatory reaction." When a basal metabolic rate was checked at -7, desiccated thyroid 0.06 Gm. a day was started along with wheat germ oil capsules. The patient was discharged on the sixth hospital day.

On March 26, 1942, the patient reported only slight spotting and slight cramps at rare intervals. Examination showed the nonpregnant uterus to be low in the pelvis on the left, and the fetus on the right to be presenting by vertex. On April 23, 1942, the fetus presented by the breech. Because of the danger of premature labor and in view of the patient's course, no attempt was made either to dislodge the nonpregnant uterus out of the pelvis or to do an external version.

On June 10, 1942 labor began. The fetus still presented by breech and the nonpregnant uterus remained incarcerated in the pelvis obstructing the birth canal. The cervix on the right was 1 to 2 cm. dilated. A low cervical type cesarean section was performed 7 hours after the onset of labor, the indication being incarceration of the nonpregnant uterus in the pelvis with breech presentation.

At operation the anomaly of the uterms was demonstrated to be a septate uterus with pregnancy in the right side. The nonpregnant side was low in the pelvis, the size of a 2 to 3 months' pregnancy. A 2,455 Gm. infant was delivered.

The postoperative course was uneventful and no additional tissue was passed from the left half of the uterus. The patient was discharged on her 14th day. At a subsequent visit the uterus was found to be well involuted and she reported that her menstrual periods were now practically painless.

During the past ten years at the New Haven Hospital obstetric admissions have totaled 9,822 and gynecologic 6,442. Nine cases, six obstetric and three gynecologic, of lack of fusion of the müllerian ducts were found; making the incidence of the anomaly about 1 in 1,500 obstetric, and 1 in 2,000 gynecologic patients. Abstracts of the remaining eight cases are presented here in abbreviated form.

Case 2.—M. E. J., a 41-year-old white primigravida married for one year, was examined first by her physician and told that she had a double uterus. History negative except for an appendectomy 20 years ago and removal of an ovarian cyst 14 years ago. In the fourth month of her pregnancy she passed a decidua from the right uterus with slight bleeding and cramps; during this time she was kept in bed for 4 to 5 days. In her sixth month she developed bronchopneumonia and was in the hospital for 9 days. Physical examination on admission at the time of labor was negative except for the pelvic examination, which revealed a vaginal septum with a separate uterus on each side, the left side being the pregnant side. A labor of 10 hours was concluded by low forceps after incision of the septum, which held up the head in the second stage. The baby weighed 7 pounds and 10 ounces.

Case 3.—M. C., a 30-year-old white para iii, gravida iv, was admitted October 10, 1941. Last menstrual period was given as July 16, 1941. She attempted abortion by medication, bleeding one day in August, September, and on October 8th passed some tissue; then spotted until admission to the hospital because of lower abdominal cramps. Physical examination was negative except for the pelvis, and evidence of rheumatic heart disease. Pelvic examination showed the cervix to be normal, some perineal relaxation, the fundus to be in midposition with a mass in the right adnexal region estimated at 8 to 10 cm. across, soft and fluctuant. The left adnexal region was negative. The preoperative diagnosis was question of abortion, complete, with right ovarian cyst or an ectopic pregnancy. At operation the patient was found to have a bicornuate uterus with pregnancy in the right horn, but the specimen had been nearly removed before the operator recognized the anomaly. Subtotal hysterectomy was performed. The pathological report was "bicornuate uterus with pregnancy in the right horn, normal endometrium in the left horn (no decidua)." (By the time the specimen had been removed there was partial separation of the placenta. We shall never know whether all the bleeding occurred from the passage of the decidua from the nonpregnant horn, or whether the operator was dealing also with an inevitable abortion.)

Case 4.—R. D. G., a 21-year-old white primigravida, had an incomplete double vagina and a double uterus with pregnancy on the right side. At operation the left side was slightly larger than a normal nonpregnant uterus. Cesarean section was done followed by a supravaginal hysterectomy.

Case 5.—Baby W., a premature of 1,965 Gm., was born with multiple defects, including a "uterus bicornis and a bifid vagina." Death occurred after 22 hours.

Case 6.—E. T., a 26-year-old white para 0, gravida iii, was seen with her third abortion at 3 months and was examined during her clinic visits by five different doctors; however, no one discovered the anomaly. It was not until the examination under anesthesia that the diagnosis of "uterus didelphys" was made. The patient had a double vagina, double cervix, and double uterus with the pregnancy and incomplete abortion being on the left.

Case 7.—J. K., a 46-year-old white nullipara, married for one year, was admitted with the complaint of dyspareunia. Pelvic examination showed a double vagina, both sides inadequate for coitus, two cervixes and two uteri. The septum was excised with relief of symptoms.

Case 8.—E. C., a 29-year-old para ii, had her first baby in 1939, at which time a diagnosis of "uterus didelphys" was made. Two cervixes were described in the history. Pregnancy, resulting in a 2,665 Gm. female infant, was complicated by mild pre-eclampsia. The patient had a spontaneous delivery after a labor of only two hours.

In 1942, with her second pregnancy, toxemia recurred in the eighth month. Pelvic examination showed vestiges of a vaginal septum and some irregularity of the fundus, at that time 2 to 3 months pregnant, which suggested a "bicornuate uterus." After a two-and-one-half-hour labor the patient was again delivered spontaneously of a 2,605 Gm. female. Diagnosis again recorded as "uterus didelphys."

To clear up the diagnosis, the patient was sent for, and vaginal examination revealed the second examiner to be essentially correct. A vestige of a vaginal septum was found in the vaginal vault, a single cervix and a "bicornuate uterus," each horn being easily demonstrated with a sound.

Case 9.—C. W., an 18-year-old white single girl, was admitted twice for pyelonephritis complicated by the absence of the left kidney. During the second admission a D. & C. done for menorrhagia revealed hyperplasia of the endometrium, a double cervix and a double uterus. On the third admission, a supravaginal hysterectomy was performed because of continued profuse uterine bleeding.

A review of the literature in recent years gives a total of 262 cases of these types of uterine anomaly. These may be summarized as follows:

Total cases	271
Obstetric	265
Gynecologic	6
Cesarean sections—total number	47
Corrected	41
Percentage—corrected	15.5%
Abdominal operations	
Obstetric—Exc. cesareans	8
Gynecologic	4
Incarceration of nonpregnant horn	12 or 4.5%
Maternal deaths	4 or 1.5%
Abortions—Smith, low quotation	12.8%
Schauffler, high quotation	53.0%
Average, DeLee and others	25.0%

Discussion

The diagnosis of congenital malformation of the female genital tract due to lack of fusion of the müllerian ducts is not usually made until

pregnancy takes place, although rarely dyspareunia is the presenting symptom. The condition is often overlooked and a patient may pass through pregnancy without difficulty. More often a pelvic mass is made out and the patient subjected to a laparotomy which may lead to the loss of all the pelvic organs, sometimes before the operator is aware that he is dealing with an anomaly and not a pathologic entity.

The presence of any vaginal anomaly should lead one to suspect further anomalies of the genital and possibly of the urinary tract. The exact type is often difficult to make out by means of bimanual palpation alone. Injection of a nonopaque medium, if the patient is not pregnant, will aid in determining the exact nature of the uterine lack of fusion. However, during pregnancy all the dangers of infection in a pregnant or pseudopregnant uterus, as in the nonpregnant horn, are encountered. When a rudimentary horn or vagina exists, the possibility of hematometra or hematocolpos is also present. As pointed out by Miller,³ regular menstruation does not rule out hematometra in a rudimentary horn.

Pregnancy.—The incidence of abortion in cases of uterine anomaly is about 25 per cent, although Findley,⁴ whose series numbered 135 cases, reported the somewhat higher incidence of 39.6 per cent. Schauffler⁵ found an incidence of 53 per cent. Since some cases of abortion may be due to an unrecognized anomaly, the higher figures may be more accurate. Premature labors are frequent, although no statistics on this point are available. A case reported by Oker-Blom, quoted by Findley,⁴ may shed light on the reason for the high incidence of abortion in these cases. This patient had a double uterus, one horn being smaller and poorly formed. Five pregnancies in the larger horn went to term, while four pregnancies in the smaller horn ended in abortions. Schauffler⁵ states that uterine septa and poorly vascularized irregularities of the fundus are responsible for the high incidence of abortions in these cases.

The anomaly has been reported by some writers as enhancing the chance of pregnancy, but Smith⁶ came to the conclusion that there was a decreased tendency, basing his statement upon a comparison of the average age of primigravidas and the length of time between marriage and pregnancy in his cases, as compared with controls.

Even after the danger from abortion has passed, the anomaly may still be a source of difficulty in pregnancy; such difficulty may vary from malposition of the fetus to rupture of the uterus. The latter, fortunately, has been rarely encountered.

Management in Pregnancy.—The proper management of the antenatal period and labor should be emphasized. Although in actual figures incarceration of the uterus occurred in only 4.5 per cent of the cases, one can read between the lines in many reports and question many more; especially when such reasons for cesarean section were

given as "failure of the head to descend" or "breech presentation." In early pregnancy, if the nonpregnant horn is palpated, it can be followed more easily during pregnancy as noted by Schauffler.⁵ In the case here reported in detail this was borne out. Findley⁴ states that, "in the event of delayed labor due to an impacted nongravid uterus that cannot be dislodged, cesarean section is indicated." Theoretically this is correct, but search of the literature fails to reveal any report of manual displacement at the time of labor. It might not be without risk due to the possibility of rupturing the uterus. Also, if the uterus failed to rise by itself, it probably would be impossible to raise it out of the pelvis after it had become moulded in place at term. If an attempt were to be made, it would seem that during the sixth or seventh month would be the best time. However, with the possibility of premature labor, that too seems ill-advised, and it is for just that reason that the author did not manipulate the uterus in the case here reported. Schauffler⁵ quotes others in the opinion that even though the uterus remains deep in the pelvis, it may not necessarily cause absolute dystocia or serious harm. In the case of a vertex presentation, which finally engaged after a trial labor, this statement may be agreed with, but in the case of breech presentation it would seem that cesarean section is absolutely indicated. Schauffler⁵ reports four breech presentations in his fifteen cases, but no incarceration of the nongravid uterus in any of these. Cesarean section was done because of the anomaly in 15.5 per cent of the cases collected, while eight additional cases had laparotomies for other reasons. This would seem at variance with the statement seen frequently in the literature that the management of pregnancy and labor in the double uterus should not differ from that of pregnancy in the normal uterus save in the event of complications. The condition itself is a complication of pregnancy and should be regarded as such. In Findley's⁴ series of 135 cases with a total of 217 deliveries, only 38.2 per cent of the deliveries were spontaneous while Falls⁷ reported major operative procedures in eleven out of fifteen cases. Any condition which results in as high as 53 per cent abortions, frequent premature labors, and then runs the gamut of operative obstetrics must be considered seriously. In handling these cases in labor it should be remembered that the cervix may be poorly formed, the musculature of the uterus may be irregular, poorly vascularized, thin and irregularly disposed while the stroma may be inadequate. A point particularly emphasized by Falls⁷ is that the fetal heart rate may become irregular during labor, probably on the basis of poor vascularization of the uterus, and this he considers an indication for cesarean section.

Third Stage of Labor.—In the event of spontaneous delivery the placenta often fails to separate, 37.9 per cent manual removals being reported by Smith.⁶ This may well be due to irregularities of contour, insertion of the placenta on a septum or faulty contraction of a poorly

formed fundus. In the event of spontaneous separation of the placenta, post-partum hemorrhage is not infrequent, Smith⁶ reporting 20 per cent in which uterine packing was necessary. Insertion of the placenta on an intrauterine septum or faulty arrangement of the musculature most certainly accounted for many of these hemorrhages.

Physiology.—Severe dysmenorrhea has been reported often in these cases. However, one of the most interesting problems is presented by the nonpregnant horn of the uterus and its decidua. Findley⁴ stresses the independence of function as evidenced by menstruation in the non-gravid uterus. Only one such case was found in the literature here reviewed. Schaffner⁵ reported bleeding in three of his cases in which the pregnancy was carried to term and consistently in those who aborted. It is conceivable that the three who bled and were carried to term were bleeding from the nonpregnant horn. DeLee¹ states that the decidual cast may be expelled and the pregnancy continue on the other side, but that usually it comes away in the puerperium. In the cases reviewed the matter was ignored except for a statement of Schaffner⁵ that "when bleeding occurs it should be considered as reflecting damage to chorionic tissue of the pregnancy itself and should call for measures combating threatened abortion." This is a reasonable attitude, but he further says that, "bleeding and bleeding with cramps are never to be regarded as harmless because it may be thought to originate in the accessory horn." The latter statement seems radical, for two out of the four cases in our small series of six cases in pregnancy had bleeding due to harmless passing of a decidual cast from the nonpregnant horn. The reason for the expulsion of the cast seems to be pressure from the expanding pregnant horn. This is the more plausible in those cases in which incarceration of the nonpregnant horn takes place. It is a matter of interest that apparently the decidua once expelled does not reform, for neither of our cases expelled decidua in the puerperium.

Morbidity and Mortality.—Maternal morbidity was reported by Smith⁶ as 30.7 per cent and was obviously due to the high percentage of operative deliveries. In the reported cases from the literature there were four maternal deaths, an incidence of 1.5 per cent. Fetal mortality was reported by Smith⁶ as 2.8 per cent corrected, 14.2 per cent uncorrected.

Conclusions

1. Duplication of the female genital tract due to lack of fusion of the müllerian ducts may be a formidable complication of pregnancy.
2. Simplification of the terminology in lack of fusion of the müllerian ducts seems necessary and a classification is here suggested.
3. Incarceration of the nonpregnant uterus with a breech presentation at term is an absolute indication for delivery by cesarean section.
4. Bleeding during gestation in a patient with duplication of the

uterus should be always carefully investigated. It may be due to passage of a decidual cast and not indicative of a threatened abortion.

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OBSERVATIONS ON THE ELDERLY PRIMIGRAVIDA

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THE presence in the hospital of an elderly primigravida is usually the cause of considerable anxiety to the attending physician, and doubts are frequently expressed as to the successful outcome of the pregnancy and labor. Are there valid reasons for the doubts and the anxiety?

In an effort to answer these questions, we have reviewed the records of primigravidas 35 years of age and over delivered at the Elizabeth Steel Magee Hospital during the five-year period between February 1, 1937, and February 1, 1942.

During this period there were 15,079 deliveries. One hundred and ninety-nine (1.32 per cent) were primigravidas 35 years of age and over. Most (108) of these were in the 35- to 36-year-old age group. Thirty-one patients were 40 or over, and of these the two oldest were 44 years of age. There were two sets of twins. Ward cases constitute approximately 50 per cent of all hospital patients, but only 17 (8.5 per cent), of whom seven were negroes, of the elderly primigravidas were of ward status. This is probably accounted for by the fact that most women in the lower economic bracket marry and beget offspring early. Therefore, the problem of the elderly primigravida is essentially that of the private physician and not the charity hospital.

The methods of delivery shown in Table I were employed.

TABLE I

Spontaneous	26	(13.2%)
Low forceps	86	(43.6%)
Midforceps	18	(9.1%)
Version and extraction	20	(10.2%)
Breech extraction	16	(8.1%)
Cesarean section	28	(14.2%)
Cesarean section with hysterectomy	3	(1.6%) (15.8%)

Not included are the two sets of twins. One set was delivered by breech extraction and version and extraction, and the other set spon-

taneously and by breech extraction. Dührssen's incisions were employed once and Piper forceps were applied to the aftercoming head in four instances.

When series of cases are published with a lower operative percentage than ours, yet with explanations and almost apologies on the part of the author for the incidence of operative procedures, we find it difficult to understand the rationale of these apologies. We have found, especially in the case of elderly primigravidas, that being "radical" early may be the most conservative procedure in the end. This hospital is almost exclusively limited to obstetrics and gynecology, and consultation is required for any suspected pathology or for any procedure other than low forceps. A better opportunity is thus offered for anticipation of difficulties than is present in most general hospitals. We are neither ultra-conservative nor radical, tending toward a middle-of-the-road policy, and we teach the medical students and resident staff accordingly. For the five-year period mentioned, cesarean section accounted for 4.54 per cent of all deliveries, version and extraction for 5.3 per cent, and spontaneous delivery for 55.22 per cent. We feel that elective cesarean section or version and extraction, while circumstances are ideal, is far better than to allow patients to have prolonged labors followed by difficult operative methods as a last resort. Only seven of the thirty-one sections in this series were in labor at the time of operation and none had prolonged labor with ruptured membranes. Obviously, version and extraction was performed while conditions were good since there was no instance of ruptured uterus. Many times it was used electively. It is easier and safer to stay out of trouble than to get out of it, once you are in. We acknowledge of course as a basic concept that the safety of the mother is paramount, but if, with this basic concept in mind, we feel we can also get a living baby, we do not hesitate to use operative procedures under ideal conditions. We do not offer excuses for the percentage of sections (15.8 per cent), or versions and extractions (10.2 per cent) in this series although almost 4 and 2 times greater, respectively, than the normal for all patients delivered in the hospital. Our results speak for themselves. With a woman of 35 or over, pregnant for the first time, the child is very important, and we frankly acknowledge that age may be the deciding factor in influencing us to resort to certain elective operative measures.

In analyzing the thirty-one cesarean sections, the indications were as shown in Table II.

TABLE II

Cephalopelvic disproportion	15	Chronic nephritis	1
Rheumatic heart disease	3	Coronary heart disease and fibroids	1
Degenerating or necrotic fibroids	3	Marginal placenta previa	1
"Elderly primipara"	2	Partial separation of the placenta	1
Quiescent pulmonary tuberculosis		Pre-eclampsia	1
with flat pelvis	1	Breech presentation	1
Tuberculosis of hip with naegle pelvis	1		

The factor of age came into play in at least nine of the sections done for disproportion, clinical judgment being placed ahead of x-ray evidence in four cases. As regards many of the other indications, the age of the patient was the deciding factor. Vaginal delivery might have been attempted had the patient been much younger. The opportunity to sterilize (4 cases) and perform myomectomy (1 case) was an added although not a deciding influence. Cesarean section followed by hysterectomy was performed in three cases, not due to prolonged labor and misjudgment of the size of the pelvis, but for necrotic fibroids in two instances and coronary heart disease with intramural uterine fibroids in the third case.

Turning now to the complications (Tables III, IV and V) found in the elderly primigravidas, one is astounded at their number and scope. The diseases of middle age have appeared. The friability and inelasticity of the tissues is evident. Such conditions are truly proof that the elderly primigravida warrants unusual care and attention.

TABLE III. COMPLICATIONS OF PREGNANCY

Premature labor at 5½ to 7 months	7
Fibroids	14
Essential hypertension	3
Nephritic toxemia	7
Eclampsia	3
Pre-eclampsia	9
Hyperemesis	4
Hydramnios	1
Rheumatic heart disease	3
Coronary heart disease	2
Pyelitis	3
Tuberculosis (hip, pulmonary)	2
Pneumonia	1
Syphilis	2

TABLE IV. COMPLICATIONS OF LABOR

Uterine inertia	34
Cervical stenosis	3
Partial separation of placenta	4
Marginal placenta previa	2
Prolapsed cord	3
Amnionitis	1
Retained placenta	1
Postpartum hemorrhage	5
1° Laceration of perineum	11
2° Laceration of perineum	12
3° Laceration of perineum	11
Complete	5
Sphincter fibers	6

The large increase in the number of complications of pregnancy in this age group over the usual run of obstetric cases is self-evident. Fibroids in fourteen patients, toxemias early or late in twenty-three patients, heart disease in five patients, all occurring in a series numbering only 199! Five per cent of the elderly primigravidas in this series either went into labor spontaneously and delivered before the fetus weighed more than 1,300 grams, which can be considered below the age of "viability," or were induced for maternal indications. There were seven cases of spontaneous premature labor at 5½ to 7 months' gestation, and three other patients had labor induced at this stage because of eclampsia, nephritic toxemia and intrauterine fetal death respectively.

In analyzing the complications of labor (Table IV), inertia and third-degree lacerations stand out. On reviewing the length of labor, it was found that the average for the 168 patients with vaginal deliveries was 17.4 hours. The shortest labor lasted 2 hours and 8 minutes, the longest 105 hours. Although only thirty-four instances of inertia are recorded among the complications, forty-nine patients (29 per cent) had labors of more than 18 hours, generally considered to be the average in a primigravida.

There were eleven third-degree lacerations of the perineum, despite episiotomies in most instances, which demonstrates how age increases the friability of the tissues. Midline episiotomy is not to be recommended in the elderly primigavida, but rather deep posterolateral incision. There were only 13 intact perineums following the 168 vaginal deliveries.

The postpartum complications (Table V) appear normal.

TABLE V. COMPLICATIONS OF PUERPERIUM

Lochiometra	3
Endometritis	3
Pyelitis	2
Pyelonephritis	1
Thrombophlebitis	1
Lobar pneumonia	1
Mastitis	1
Parotitis	1
Rectovaginal fistula	1

The average postpartum hospital stay was but 14 days, the shortest being 9 days and the longest 66 days—the latter due to thrombophlebitis. Only eight patients were hospitalized for 20 days or over following delivery.

An analysis of morbidity in accordance with the classification of Ziegler and Austin,¹ i.e.,

(1) Afebrile Zone—99° F and under

(2) First Febrile Zone—above 99° F and below 100.4° F

(3) Second Febrile Zone—100.4° F and above for 2 consecutive days excluding the first 24 hours, gives us the following:

There were 84 (42.21 per cent) afebrile patients; 84 (42.21 per cent) in the first febrile zone and 31 (15.58 per cent) in the second. This compares with the Elizabeth Steel Magee figures for the year 1937 of 48.47 per cent, 42.37 per cent, and 9.16 per cent respectively, as cited by Ziegler.¹

What of the infants of these elderly primigravidas? Males predominated in the ratio of 108 to 89 (plus 2 sets of male twins) and in patients over 40, the ratio was 18 to 13. The weights varied from 700 grams to 4,945 grams. There were 26 premature infants which weighed less than 2,500 grams. Ten infants weighed 4,000 grams or over. Only three infants presented abnormalities. These deformities were talipes equinovarus, talipes equinovagus, and hemimelia.

In the final analysis, maternal and fetal mortality is the measuring stick of any method of handling a group of patients. Recently Wahrsinger and Kushner² reported a series of one hundred eleven patients with a maternal mortality of 2.7 per cent and a gross fetal mortality of 9 per cent. They cite a report presented by Nixon with 4 per cent and 17 per cent for the respective mortalities although no sections were done, as well as a report by Linden with no maternal mortality but 4 per cent craniotomies. In our series no mother died, but nineteen infants were lost, a gross fetal mortality of 9.5 per cent. As stated above, ten infants can be classified as "nonviable" due to the period of gestation and four others were macerated (the mothers of three of these were aged 41 years or over, and one had a section and hysterectomy for a necrotic fibroid, fetal heart sounds being absent prior to operation). The corrected fetal mortality is therefore 2.7 per cent. Of the remaining five infants, two were premature, weighing 1,925 and 1,975 grams re-

spectively; in the latter, the mother had labor induced for severe pre-eclampsia. The infant was stillborn. Of the three full-term babies, one, following low forceps delivery, died on the third day due to a tentorial tear; a second was stillborn following a difficult version and extraetion, probably from the same cause; and the third died of hemorrhagic disease of the newborn on the third day after birth. It was delivered by midforceps because of maternal eclampsia.

Conclusions

A series of 199 elderly primigravidas delivered over a five-year period at a teaching maternity hospital is reported. This group comprises 1.32 per cent of total deliveries. There was no maternal mortality, a gross fetal mortality of 9.5 per cent, and a corrected fetal mortality of 2.7 per cent.

The elderly primigravida 35 years of age or over, is more subject to:

- (1) Loss of the fetus at 5 to 7 months—before “viability”
- (2) Premature labor
- (3) Degenerative diseases
- (4) Early or late toxemias of pregnancy
- (5) Inertial labors
- (6) Third-degree lacerations

With these complications in mind, more careful attention is needed to continue the pregnancy and more elective obstetric procedures may be needed at term to effect delivery. It is important, if operative interference is deemed necessary, that it be instituted as early in labor as feasible before the ideal time, as regards the safety of mother and infant, has passed. Individualization of patients is an absolute necessity.

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THE LOCAL USE OF ACID MEDIA AND SULFA DRUGS IN THE MANAGEMENT OF CERVICITIS AND VAGINITIS

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FROM 1936 to 1940 the local use of anhydrous lactose as a pH factor was studied and reported.¹ This anhydrous sugar applied as a vaginal pack produced buffered acids through bacterial decomposition encouraging the acid flora, Döderlein bacilli and inhibiting the pyogenic cocci by creating an environment pH 4.5.

It remained to be seen if by adding local sulfa drugs, further differential action could be obtained. Sulfa drugs are neutralized by the para-aminobenzoic acid present in pus.² Therefore, when pus is found in the cervix and vagina, a large concentration of sulfathiazole or sulfanilamide is needed locally to produce any bacteriostatic effect. Such factors as surface tension adhesiveness, and confining ability of the media were found to be of great importance when sulfa drugs were added. Contact of the sulfa drug with the surface lesion must be maintained constantly to be effective.

Sulfathiazole showed no clinical evidence of absorption from either cervix or vagina. One patient, who had a dilatation and curettage as well as an extensive conization of the cervix, had 30 grams of sulfathiazole powder packed into the cervix and vagina. Subsequent blood level concentration showed 0.3 mg. per cent. Another patient under identical conditions had 30 grams of sulfanilamide packed into the cervix and vagina, and showed a blood level concentration of 0.7 mg. per cent.

Sodium sulfathiazole, the sodium salt of sulfathiazole with a pH 9.6 to 12.0, caused sloughing of the cervical mucosa in ten cases and cervical erosion in twelve patients and could not be used alone. When combined with an acid medium or acid vehicle, it became sulfathiazole, losing its sodium ion.

Methods of application of sulfa drugs alone and in suitable vehicles have had our attention for the past two and a half years. Sulfanilamide is less effective in cervical and vaginal nonspecific infections than sulfathiazole. Sulfathiazole is also specific for the gonococci.

Conization of the cervix is the method of choice in removing cervical tissue containing nabothian cysts and infected glands.³ The remaining cervical tissue must recover from the burn inflicted at the time of conization. The effect of sulfa drugs in burns is well established.⁴

Sulfa drugs used alone in the vagina did not encourage the growth of acid vaginal flora, or retard the Döderlein bacilli in any way, if sugar or buffered acid jellies were also used. When sulfathiazole was mixed with beta lactose as a powder, insufficient concentration or

application of the sulfa drug resulted, and little or no improvement was noted over the use of the sugar alone for conization or vaginitis application. But when sulfathiazole was used alone as a cervical pack and filled the newly coned area of the cervix, and when such a sulfa pack was held in and against the cervix by a vaginal pack of beta lactose, marked clinical improvement in the rate and character of cervical healing after conization was noted in all cases. This procedure was done as a routine on all conizations, and the cervix cleaned and repacked with sulfathiazole and the vagina with beta lactose two times a week for the first two weeks postconization.

At the American Congress on Obstetrics and Gynecology in St. Louis, April, 1942, Dr. Dudley Smith and the author presented a scientific exhibit on the use of sulfathiazole at the time and following conization of the cervix and coagulation of Skene's ducts in selected cases of acute gonorrhea, which did not respond to oral administration of sulfathiazole.⁵ Twelve such patients who had received one gram of sulfathiazole four times a day for five days, for two or more such courses of therapy, still persisted in positive urethral and cervical cultures, and were subjected to conization of cervix and destruction bilaterally of Skene's ducts by surgical diathermy. Local sulfathiazole was used as in Table I on eight cases, and on four cases with buffered acid jelly, as shown in Table II. There was no morbidity noted in this rather radical procedure and eleven cases became free from the gonococci as demonstrated by repeated cultures. Only one patient later developed a positive urethral and cervical culture; she had had insufficient removal of cervical tissue at the time of conization. No greater test could be used to prove the effectiveness of sulfathiazole and a buffered acid medium of pH 4.5.

Since May, 1942, all cases of cervicitis and vaginitis, as well as pre-operative and postoperative conizations, have had buffered acid jelly applied as the vehicle for sulfa drugs. The formulas were as follows:

Sulfonamide Jelly (Gyn.), No. 151-3-B-2

200 mesh sulfanilamide	5.0%
200 mesh sulfathiazole	5.0%
Tragacanth flakes	3.0%
Granular boric acid	3.0%
Glycerin	10.40%
Powdered acacia	2.0%
Potassium hydroxide solution	18.8%
4.5 c.c.	
Water	100.0%
pH adjusted to 4.0 with acetic acid	

Sulfonamide Jelly (Gyn.), No. 151-3-B-4

200 mesh sulfanilamide	10.00%
200 mesh sulfathiazole	10.00%
Tragacanth flakes	3.00%
Granular boric acid	3.00%
Glycerin	10.00%
Powdered acacia	2.00%
Potassium hydroxide solution	18.8%
Distilled water	100.00%
pH 4.5 (actually 4.42)—adjusted with acetic acid	

TABLE I. CERVICAL CONIZATION FOLLOWED BY SULFATHIAZOLE* PACK

DESCRIPTION OF POSTOPERATIVE CERVIX HEALING PROCESS IN WEEKS		AVERAGE AGE		AVERAGE PAIN	DESCRIPTION OF CERVICAL LESION PREOPERATIVELY		
		33		3	32 Old chronic cystic cervicitis 22 Erosion, papillary with cystic change 20 Laceration with erosion early cystic change		
		HEMORRHIAGE		2 cases	TYPE OF VAGINAL SMEAR	VAGINAL pH	CERVICAL pH
		PRIMARY	SECONDARY				
1. 74 cases, gray membrane and slough	10 cases	1 case		2 cases	Type III	pH 7.0	pH 8.0
2. 70 cases, gray membrane and slough	8 cases				Type III	pH 7.0	pH 8.0
3. 40 cases, granulation clean	1 case				Type II	pH 6.0	pH 7.0
4. 50 cases, granulation clean with epithelization beginning					Type II	pH 5.5	pH 7.0
5. 70 cases, epithelization, complete					Type I	pH 5.0	pH 8.0
6. 73 cases, epithelization, complete					Type I	pH 4.5	pH 8.0
7. 74 cases, epithelization, complete					Type I	pH 4.5	pH 8.0
8. No stenosis, but cervical canal dilated					Type I		

*Winthrop Chemical Company, Inc., furnished the sulfathiazole powder for this series.

TABLE II. CONIZATION FOLLOWED BY SULFA DRUG IN ACID JELLY*

DESCRIPTION OF POSTOPERATIVE CERVIX HEALING PROCESS IN WEEKS	BLEEDING MILD	AVERAGE AGE		DESCRIPTION OF CERVICAL LESION PREOPERATIVELY		
		PRIMARY	SECONDARY	TYPE OF VAGINAL SMEAR	VAGINAL pH	CERVICAL pH
1. 38 cases, gray membrane	2 cases	1 case	1 case	Type III	pH 6.0	Average pH with nitrazine paper
2. 16 cases, gray membrane and slough	2 cases			Type II	pH 5.5	
3. 30 cases, granulation clean with epithelization beginning				Type II	pH 5.0	
4. 37 cases, epithelization, complete				Type I	pH 4.5	
5. 38 cases, epithelization, complete				Type I	pH 4.5	
6. No stenosis						
7. — weeks —						
8.						

*Ortho Products, Inc., furnished material using: 151-3-B-2 Sulfa Jelly 10% (5% each of sulfathiazole and sulfanilamide), pH 4.0; using 151-3-B-4 Sulfa Jelly 20% (10% each of sulfathiazole and sulfanilamide), pH 4.5. Ten of the 38 patients had 10% sulfa jelly. 28 cases had 20% sulfa jelly used throughout, ten of the 16 cases which had gray membrane and slough at two weeks, had been on 151-3-B-2 (10% sulfa jelly) and the remaining six cases were treated with 151-3-B-4 (sulfa jelly 20%).

TABLE III. CONIZATION FOLLOWED BY ACID JELLY*

DESCRIPTION OF POSTOPERATIVE CERVIX HEALING PROCESS IN WEEKS		BLEEDING MILD	AVERAGE AGE		AVERAGE PARA		DESCRIPTION OF CERVICAL LESION PREOPERATIVELY			
			PRIMARY	SECONDARY	TYPE OF VAGINAL SNEAR	VAGINAL pH	CERVICAL pH	Average pH with nitrazine paper		
1.	6 cases, gray membrane and slough with odor	2 cases					Type III	pH 7.0	pH 7.0	
2.	6 cases, gray membrane and slough with odor	2 cases					Type III	pH 6.0	pH 8.0	
3.	6 cases, granulation and slough	1 case					Type III	pH 6.0	pH 8.0	
4.	4 cases, granulation clean						Type III	pH 6.0	pH 8.0	
5.	3 cases, epithelization, complete						Type II	pH 5.5	pH 7.0	
6.	4 cases, epithelization, complete						Type II	pH 5.5	pH 8.0	
7.	6 cases, epithelization, complete						Type I	pH 5.0	pH 8.0	
8.	1 case of stenosis									

A routine in the cervicitis clinic is to apply with vaginal applicator mixtures of sulfathiazole and sulfanilamide in buffered acid jelly pre-operatively, at the time of conization, and postoperatively. Usual instructions to the patient are nightly vaginal applications of the jelly (5 to 10 c.c.) for the first two weeks, then every other night for the next two weeks, even though the patient were menstruating. Nightly applications during any period of bleeding or regular menses were insisted upon. Douches are prohibited, and intercourse forbidden. Table II summarizes thirty-eight cases of conization so treated with the above formulas.

The mechanical adhesiveness, yet free flow and capillarity of the jelly is necessary if the sulfa drug is to be efficiently applied to the cervix and vagina in this water soluble medium. The jelly flows into the conical area of the cervix and bathes the coned surface with the thick creamy sulfa drug and thus maintains closer application than was possible when the sulfa drugs were applied as a powder by blower, and the anhydrous sugar applied as a vaginal pack to hold it in place in the vaginal vault. The buffered acid jelly with the sulfa drugs has the additional advantage of patient self-application by means of a vaginal applicator. Clinical results show a marked improvement over any previous method studied.

When conization of the cervix has removed the disease-gland-bearing area of the cervix and the latter is healed, the vaginitis will be under control, and in most cases the patient will remain symptom-free from pyogenic infections of the vagina, if there is a normal estrogenic type of vaginal mucosa.

Vaginitis Study

There were patients with minor cervical erosion in which no morbid anatomy of the cervix existed, yet vaginitis was present. By definition there are three types of vaginal smears as follows:⁶

Type I, pH 4.0 to 5.0, Döderlein bacilli in abundant vaginal epithelium (desquamated)

Type II, pH 4.7 to 6.0, few Döderlein bacilli, few vaginal epithelial cells, trichomonads and few pyogenic organisms.

Type III, pH 5.6 to 8.0, no Döderlein bacilli, no vaginal-epithelial cells, many cocci, colon bacilli, or other pyogenic organisms, not monilia.

These patients were grouped and treated as follows:

Twenty-eight cases received buffered acid jelly applied with vaginal applicator nightly for two weeks, then every other night for two weeks. (Fifteen per cent failure.) The formulas for this jelly are:

Glycerin	10.00%
Vegetable gum	5.00%
Boric acid	3.00%
Ricinoleic acid	0.75%
Propyl ester of parahydroxybenzoic acid	0.05%
Oxyquinoline sulphate	0.025%
Perfume	0.05%
Water to	100.00%
pH adjusted with acetic acid to 4.5	

Fifteen cases (with 12 per cent failure) received 10 per cent sulfa jelly (formula 151-3-B-2) used as above.

Eighteen received 20 per cent sulfa jelly (formula 151-3-B-4) applied with vaginal applicator nightly for two weeks, then every other night for two weeks (8 per cent failure). All patients received this therapy over the period of a menses; five of these had senile vaginitis.

In sixty-one cases of vaginitis, the cervix received no additional treatment. There was no attempt to classify the trichomonas as the possible etiologic agent. Hydrogen-ion concentration readings were taken with nitrazine paper and the Beckmann pH meter. Smears or hanging drop were used to classify the vaginitis. Cultures were taken when indicated to exclude the gonococcus, as no acute gonorrhea was included in this series.

Most of these patients were office cases, and the ages ranged from teen-age to menopause (senile vaginitis). There were added to this number (sixty-one cases), ten cases of monilia, six of which were pregnant. These were treated with self-application of buffered acid jelly alone with disappearance of the monilia in all 6 cases. Four other cases were treated with 10 per cent and 20 per cent sulfa jelly with the report of one failure. Treatment was as above (5 c.c. to 10 c.c. nightly for two weeks, then every other night for two weeks).

For the type III smear vaginitis, 20 per cent sulfa jelly (#151-3-B-4) restored a type I vaginal smear eight days quicker than when the 10 per cent sulfa jelly was used, and 14 days quicker than when the buffered acid jelly without sulfa drug pH 4.5 was used. However, buffered acid jelly alone was as effective in changing the type II smear vaginitis to type I as when the sulfa jelly was used with it. This was not the case in type III smear vaginitis which required the use of the sulfa drug. Trichomonas was most common and was seen in about 80 per cent of the persistent type II smear vaginitis. Trichomonas was not observed often in the pH 6.5 to 8.0 type II smear or hanging drop.

Thus it would seem that buffered acid jelly alone was effective in trichomonas vaginitis therapy. This observation seems to be confirmed by Allen and Baum who reported extensively on the vaginal use of buffered acid jellies, which gave symptomatic relief in 84 per cent of their cases.⁷

Discussion

There are presented here 112 cases of conization of the cervix and 71 of vaginitis. In our hands the addition of sulfa drugs to the pH factor has been as great an improvement as the pH factor was over older methods of antiseptics used 10 years ago in the management of cervicitis and vaginitis. Cervical stenosis is most notable by its absence since using sulfa drugs after conization. Mild bleeding is little if any reduced over the old beta-lactose technique. Secondary bleeding and hemorrhage is reduced, as infection is definitely less after conization. The speed of cervical healing with low morbidity is noteworthy. Three weeks for complete healing of the cervix after conization may be expected with the use of sulfa drugs in buffered acid media.

In view of the fact that buffered acid jelly containing 20 per cent sulfathiazole is experimental and not commercially available, we are also

using buffered acid jelly and vaginal sulfonamide suppositories but with less favorable results to date.

Conclusions

1. The bacteriostatic effect of sulfathiazole and sulfanilamide is demonstrated by local applications to cervix and vagina without appreciable absorption.

2. Controlling the vaginal pH to 4.0 to 4.5 by the addition of buffered acid jellies is of value in the management of cervicitis and vaginitis, especially the trichomonas type of vaginitis.

3. Combining the sulfa drugs and buffered acid vaginal jellies gives the most effective therapy in cervicitis (conization post-operative management) and vaginitis of all types.

4. Conizations of the infected cervix may be safely performed in cases of acute gonorrhea when positive cervical cultures have persisted after oral administration of sulfathiazole; providing sulfa drugs in acid media are used locally during the healing period and at the time of conization. Negative cultures will then be the rule.

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THE UTERINE CONTRACTION PATTERN OF FALSE LABOR AND ITS RELATION TO PREMATURE LABOR

A Study of 16 Patients With the Lóránd Tocograph

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ONE of the problems of false labor which bears investigation lies in distinguishing it from true labor. Beek¹ states that the false pains are irregular, that they differ from those of true labor, but lists no other distinguishing characteristics. Adair² considers the chief difference to lie in the fact that the contractions of false labor fail to advance the process of labor, and also that the contractions which occur during false labor do not increase progressively in either frequency or duration.

White³ distinguishes false from true labor according to the following criteria: (a) true pains are felt in the back while false ones are located in the abdomen; (b) true pains are regular in occurrence and are associated with a hardening of the uterus, whereas false ones occur irregularly and are not accompanied by hardening of the uterus, (c) if the internal os will admit a finger, the membranes will be felt to become tense only in the presence of true pains.

On the hypothesis that false labor might be distinguished from true labor on the basis of a significant difference in the contraction patterns, as revealed by the Lóránd tocograph, we examined the tocographic records of all of our patients who experienced painful uterine contractions during pregnancy. Information gained from this source forms the basis for the present report.

Materials and Methods

The uterine contractions which take place during pregnancy were studied in a series of 1,119 tracings secured from ward patients in the Hospital of the University of Pennsylvania between August 1, 1938, and January 1, 1943.

Records of patients in this group, who were experiencing pain in association with their contractions—and of such a degree as to result in a diagnosis of false labor—form the basis for the present report.

Results

Sixteen women supplied observations for consideration. Table I summarizes information upon: (a) the time in pregnancy at which the false labors were registered; (b) the weights of the infants at birth; and (c) the character of the contraction patterns.

The uterine contraction pattern of pregnancy can be distinguished usually from that of labor. The former, Fig. 1, may record no contractions, or waves of irregular size and shape, and ones which usually

are relatively aperiodic in occurrence. The labor pattern, Fig. 2, is composed of waves which resemble each other closely in magnitude and shape, and ones which are relatively periodic in occurrence.

Contraction Pattern of False Labor.—The contraction pattern of the patient experiencing false labor resembles that of either pregnancy or labor. The data upon the sixteen patients mentioned above are arranged in Table I according to that classification. Half of the women exhibited the pregnancy pattern, and the other half the labor pattern. The occurrence of both patterns in association with false labor suggests that the pattern is of little or no value in distinguishing between false and true labor.

The Time of Occurrence of False Labor.—Table I records: (a) the interval between the tracing of the false labor pattern and the expected date of delivery; (b) the interval between the tracing and the actual date of delivery; and (c) the weights of the infants at birth. The expected and actual dates of delivery rarely coincided, and were of little value in determining how long before term the false labors took place.

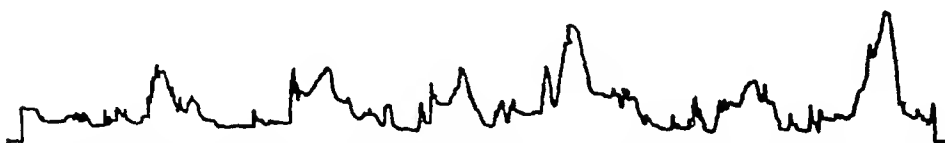


Fig. 1.—Normal pregnancy contraction pattern. Patient R. T. Tracing No. 165, made 11 days before labor. Note irregularity in size and shape of waves and their aperiodicity. The uterus of this patient was unusually active.



Fig. 2.—Normal labor contraction pattern. Same patient as Fig. 1. Tracing No. 179, made during first stage of labor. Note: A, disappearance of small waves, B, uniformity in shape of waves, C, magnitude of waves, and D, periodicity of waves.

TABLE I. PATIENTS EXPERIENCING FALSE LABOR

PATIENT		INTERVAL BETWEEN TRACING AND		INFANT BIRTH WEIGHT	TYPE OF CONTRACTION PATTERN
SERIAL NUMBER	TRACING NUMBER	DUE DATE	DELIVERY DATE		
		days	days	gm.	
1	232	8	8	3,654	Pregnancy
2	237	14	9	4,290	"
3	252	?	26	2,880	"
4	921	7	9	5,180	"
5	2,220	20	9	3,650	"
6	1,350	6	6	3,230	"
7	1,364	10	20	3,200	"
8	1,456	24	12	3,200	"
9	1,430	6	6	3,580	Labor
10	130	20	31	3,500	"
11	829	13	6	3,900	"
12	912	?	36	2,250	"
				2,640	
13	1,151	16	11	3,750	"
14	1,216	1	6	2,850	"
15	1,445	?	32	2,160	"
16	1,854	40	6	2,325	"

?: Due date in doubt.

Patient 15 experienced her false labor 32 days before she was delivered of a premature infant, i.e., weighing less than 2,500 grams. On the basis of the weight of her infant, therefore, she must have experienced her false labor considerably prior to 32 days before the date of her expected confinement.

Patient 16 was delivered of a premature infant 40 days before the expected date of her confinement. Thus it would appear that these two patients both experienced their false labors before any of the other patients in the series, patient No. 12 with twins being excepted.

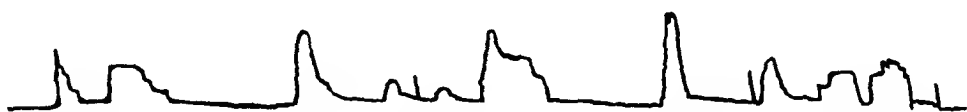


Fig. 3.—False labor showing pregnancy pattern. Patient J. A. Tracing No. 252, made 24 days before labor. Note irregularity in size and shape of waves and their aperiodicity. Compare with Fig. 1.



Fig. 4.—False labor showing labor pattern. Patient V. A. Tracing No. 1,445, made 32 days before labor. Note uniformity in size and shape of waves and their periodicity. Compare with Fig. 2.

Comment

The above observations would seem to justify the following comments: The uterine contraction pattern associated with false labor may resemble that of either pregnancy or true labor. This fact leads us to the conclusion that it cannot be employed as a means for distinguishing between false and true labor.

The untimely interruption of pregnancy is of such frequency and importance that every effort should be made to reduce its incidence. This is especially true in cases in which the patient has failed repeatedly to go to term. The present observations give rise to a thought which may aid in carrying some of these pregnancies to a normal ending.

The delivery of premature infants by patients 15 and 16, Table I, apparently followed false labors which occurred somewhat earlier than did those of patients who gave birth to full-term infants. Incidentally, although this observation may have no value, the contraction patterns of both patients resembled those of true labor. If these observations are true, they suggest that an early false labor may be followed by a premature labor. If such is the case, it would seem the part of wisdom to treat patients experiencing early false labors immediately, and perhaps at frequent intervals, with corpus luteum or other substances which have been recommended for the maintenance of pregnancy.

Summary and Conclusions

1. Tocographic records were made of the uterine contraction patterns of sixteen patients while they were experiencing false labor.

2. In some instances the contraction pattern of false labor simulated that of pregnancy, and in other cases resembled that of true labor. In view of this variability in the character of the contraction pattern associated with false labor, it is concluded that it does not offer a means for distinguishing between false and true labor.

3. Two patients experienced unusually early false labors, and gave birth to the only premature infants in the series. This association of the birth of premature infants with the occurrence of relatively early false labors suggests the advisability of treating patients who experience early false labors with corpus luteum or other substances recommended for the maintenance of pregnancy.

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PARASITIC OVARIAN CYSTS

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THE existence of ovarian cysts as parasitic tumors has been recorded by a number of observers. In 1860, Rokitansky described alterations in the vascular supply which followed torsion of the pedicle of ovarian tumors. In 1892, August Martin published a report of two interesting cases of ovarian tumors with torsion. Spontaneous amputation of the pedicle with revascularization of the mass was found at operation.

Prior to this the condition had been noted at the autopsy table. Kayser states that Morgagni described parasitic ovarian tumors as early as 1748. However, today, they are rather unusual, undoubtedly because operation is performed earlier for symptoms suggesting torsion of an ovarian tumor.

The development of parasitic tumors may be divided arbitrarily into four stages depending on the degree of diminution of the primary blood supply. They are not completely separate phases but they represent, rather, a progression to the parasitic end result.

The *first stage* of reduction in the original vascular supply is due usually to a slow torsion of the mass on its pedicle. Infrequently with ovarian tumors, but more common with other pedunculated tumors, such as uterine fibroids, this may be due to growth of the tumor to the point where the blood supply through the pedicle becomes inadequate.

The etiology of pedicle torsion has been attributed to many causes and is probably a combination of several. Growth of the mass with traction and elongation of the pedicle certainly is a predisposing factor. Sellheim¹¹ believes torsion is secondary to external stress with resultant alteration of intra-abdominal tension. Others would prefer to relate it to intestinal peristalsis, corporeal movement or congenital variations. Bass¹ points out that pregnancy, with its resultant pelvic displacements, may play an important role in some cases.

In the *second stage* adhesions between the mass and adjacent tissues or the omentum are formed. These may be stimulated by the appearance of localized areas of aseptic necrosis at the periphery of the mass, most distal to the blood supply. Geist³ has pointed out that regressive changes in the ovary are common manifestations of decreased vascularity. Thus, edema, hyaline scarring, calcification and even bone formation may be found.

The *third stage* occurs with additional torsion and the further decrease in the primary blood supply. Secondary vascularization through the adhesions follows. In this phase, the tumor becomes semiparasitic receiving its blood supply from two sources: its pedicle, and the newly formed collaterals from the vessels to the adjacent tissues.

The *fourth stage* is represented by additional torsion to the point of complete amputation of the pedicle. The tumor now takes on a completely parasitic existence. The pedicle tends to become atrophied and fibrotic. At operation it no longer may be recognized as such, and the mass, for excision, must be separated solely from the adjacent tissues.

The entire process must be a slow one to permit new vascularization prior to complete loss of the original. The various stages which follow progressive torsions probably are represented in the symptomatology presented by the patient as recurrent attacks of abdominal pain.

Among the ovarian parasitic tumors, the type most frequently seen is the dermoid. This is as would be expected, since the ovarian dermoid often is subject to torsion. Serous cysts, solid ovarian tumors and relatively normal adnexa have been reported.

The organ with which these parasitic cysts are most often associated is the omentum, where they tend to become embedded. However, they have been found attached to the uterus, the broad ligament, the bowel and the bladder. The parietal peritoneum is involved occasionally.

Most of the parasitic ovarian tumors which have been described have not been very large. However, it is possible for them to continue to increase in size after the new source of blood supply has been established. Truesdale¹² reported the removal of a parasitic cystadenoma of the ovary weighing ninety pounds. He quotes Smith as having presented a case before the Massachusetts Medical Society where the tumor weighed 192 pounds, and the primary pedicle measured no more than one-half inch in diameter.

An accurate preoperative diagnosis of parasitic cyst of the ovary has not been made. A history of repeated attacks of lower abdominal pain associated with the findings suggestive of an ovarian mass in an abnormal location may indicate its presence. Pain has been the predominant symptom in almost all of the recorded cases.

Case Report

B. H., aged thirty years, was admitted to the hospital on January 5, 1943, the first admission of a gravida 2, para 2 complaining of attacks of pain localized to the right lower quadrant. These have recurred frequently during the previous six months, but seemed to have no relation to her menses. There had been no nausea or vomiting. The menstrual periods were regular, but during the last three periods the patient had noted some hypomenorrhea. No dysmenorrhea had been present.

The patient recalled somewhat similar attacks about five years prior to the present complaints, but stated that they had subsided spontaneously. She was entirely free of pain during the interim.

Her past medical and obstetric history was irrelevant to the present condition.

Physical examination was normal except for the pelvic findings. In front of the uterus a rounded, movable, nontender mass, the size of a peach, was palpated. Posteriorly and somewhat to the right another mass, the size of an orange, could be distinguished. A third mass, the size of a walnut, was palpated laterally and to the right. The uterus could not be satisfactorily outlined. Impression at that time was probably multiple cysts of the ovaries, perhaps dermoid in origin. The possibility of pedunculated fibroids was also considered.

Laboratory Data.—Blood and urine studies were all within normal limits. Scout film of the abdomen and intravenous pyclogram were reported as follows:

“Both kidneys are normal in all respects. There are several clusters of calcification within the pelvis, one having the typical appearance of a calcified fibroid. Below this fibroid is another circular calcification which may be an additional fibroid.

"Intravenous pyelogram reveals no abnormality in either urinary tracts or urinary bladder. The calcified fibroids cause extrinsic pressure on the urinary bladder."

Operation.—Exploratory pelvic laparotomy was performed on January 9, 1943. The right ovary was found to be converted into a multilocular dermoid cyst containing three separate portions. It was attached laterally by the right infundibulopelvic ligament about which the amputated right tube was twisted. It was attached also to the peritoneum over the dome of the bladder by a pedicle. Both of these pedicles were twisted; the infundibulopelvic three complete turns, the peritoneal not accurately determined. A single smaller dermoid cyst, probably part of the right ovary, was found embedded extraperitoneally in the right lateral pelvic wall.



Fig. 1.—X-ray of the Pelvis. Arrows show circular area of calcification.

The uterus was normal in size and an amputated stump of tube about 2 cm. in length was noted coming from the left horn. Posterior to the uterus another cyst was found which, when delivered, was attached completely to the omentum by a pedicle. This was twisted $2\frac{1}{2}$ times on itself, but a new band from the omentum to the lateral aspect of this cyst was not twisted. This tissue was the size of a lead pencil and contained blood vessels, additional vascular supply to the tumor (see Fig. 2 for relationships of these cysts). The left infundibulopelvic ligament was not found.

The three cysts were removed and, after adequate peritonization of the pedicle stumps, the abdomen was closed without drainage.

Postoperative Course.—The patient made an uneventful recovery and left the hospital on the thirteenth postoperative day. When seen in follow-up clinic two months later, she was quite well, except for beginning menopausal symptoms for which estrogen therapy will be given.

Pathology.—Study of the tumors revealed the right ovary to contain two attached dermoids. It also showed marked edema, follicular cysts and a hemorrhagic corpus luteum. The parasitic cyst found in the omentum was a necrotic and calcified dermoid. However, within its wall, ovarian tissue definitely could be recognized. The third mass, the one found extraperitoneally, was also a necrotic and calcified dermoid.

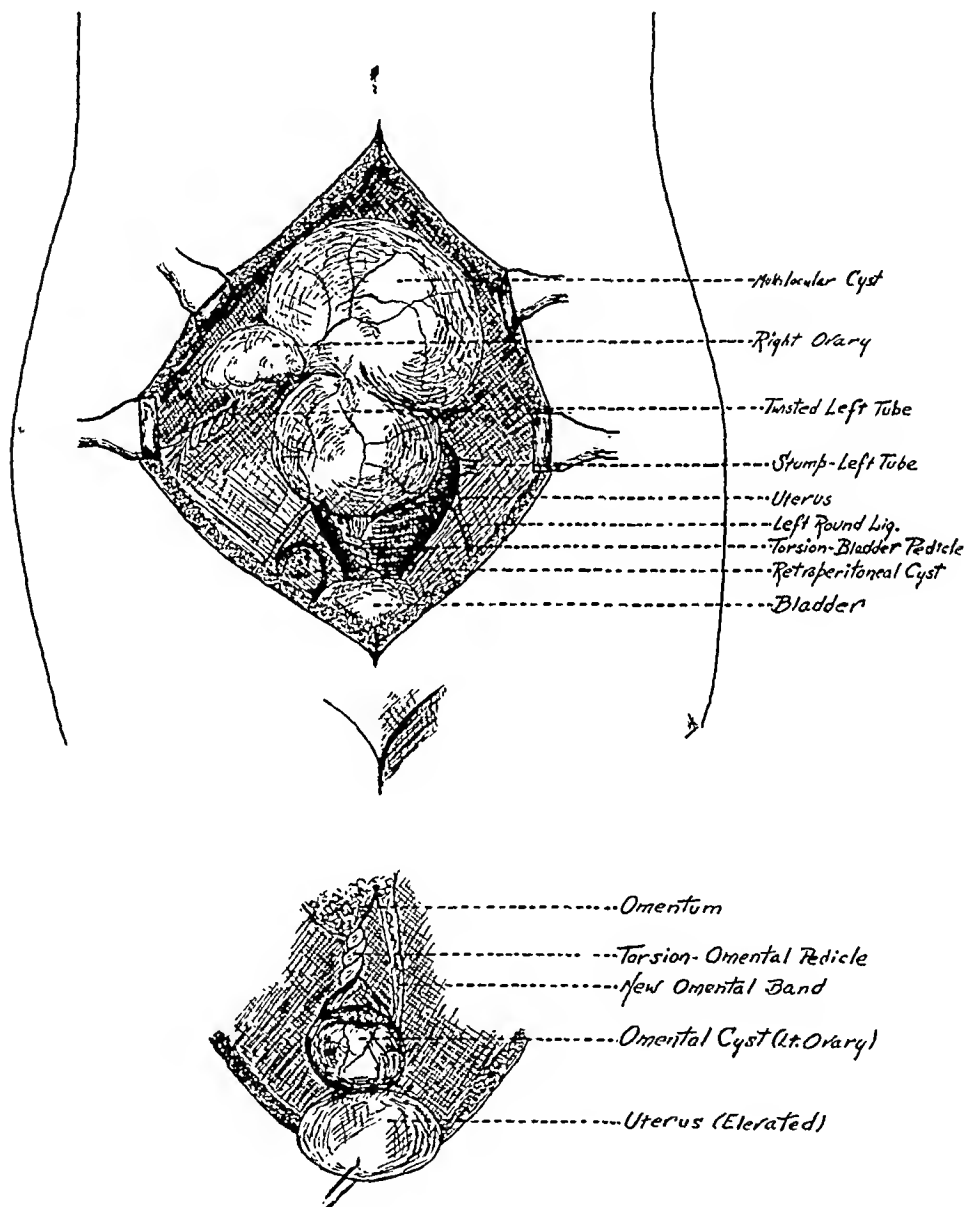


Fig. 2.—Relationship of the cysts as found at operation.

Comment

Reconstruction of the pathogenesis in the development of parasitic tumors could be done by careful examination of these cysts and their relationships. The later stages described above can be recognized in the drawing of the pelvic viscera as noted at operation. The main

portion of the right ovary was semiparasitic, the left completely so. The torsion of the omental cyst represented a beginning decrease of the secondary vascular supply. The new band of tissue suggested the beginning of the tertiary. The calcified and necrotic dermoid found in the lateral pelvic wall probably indicates the end stage of this development, a quiescent, completely parasitic, degenerated tumor. The patient's complaints of pain were amply explained by the pathology found. Because we are alert to the surgical emergency of torsion, the end result of progressive slow torsion, as represented by this case, is seldom seen.

This report incidentally may shed light on some of the unexplained omental dermoids. Almost all of the reported cases have occurred in women. We were able to establish beyond doubt the ovarian etiology in this case.

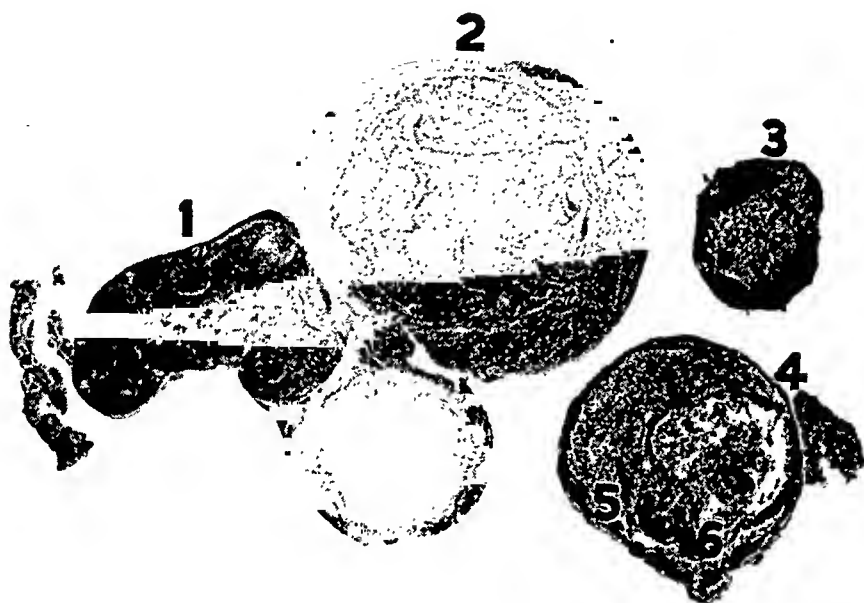


Fig. 3.—Showing 1. Right Ovary. 2. Multilocular Cyst. 3. Retroperitoneal Cyst. 4. Omental Cyst. 5. Ovarian Tissue. 6. Dermoid.

Summary

1. The literature on parasitic ovarian cysts has been briefly reviewed. Pathogenesis with arbitrary division into four stages is discussed.

2. A case with three parasitic dermoid cysts involving both ovaries has been presented.

3. The finding of ovarian tissue in the omental cyst may explain the etiology of some dermoid cysts thought to be primary in the omentum.

4. The evidence of calcification found by x-ray and histological study are indicative of the degenerative changes associated with slow pedicle torsion.

5. The case also demonstrates the process of new vascularization following pedicle torsion.

I should like to express my gratitude to Dr. S. H. Geist, and to Dr. L. Strauss for their assistance in the preparation of this report.

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CAUDAL ANESTHESIA IN ONE HUNDRED SIXTY OBSTETRIC CASES

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WE REPORT herewith a series of one hundred and sixty maternity cases delivered in the White Memorial Obstetrical Hospital in which caudal anesthesia was employed during the course of labor. A few of these cases received the anesthetic just prior to delivery, but the majority were carried for periods ranging from 2 to 28½ hours.

Of the one hundred and sixty cases in which caudal anesthesia was attempted, one hundred and twenty-nine achieved a satisfactory degree of analgesia for labor and delivery, with the exception of thirteen cases in which supplementary agents were used to finish the repair, or during forceps delivery. In twenty cases the anesthesia was judged to be partial or in some manner unsatisfactory. Most of these were due to the needle slipping out and failure in replacement, though a few patients in whom the solution had been correctly placed had moderate residual pain in the fundus with the contractions, but sufficient perineal anesthesia for delivery and repair. The eleven failures were all judged to be due to inability of the operators to enter the canal.

More than one injection through an indwelling needle was given to one hundred and eight cases; these, therefore, are classified as continuous caudal block.

The second stage of labor is prolonged due to lack of expulsive effort of the abdominal muscles stimulated by pressure on the rectum as the presenting part descends. Operative deliveries have a higher incidence in this group than in those having other types of analgesia.

Deliveries other than spontaneous without episiotomy are tabulated:

1. Episiotomy and midforceps delivery	1, a primipara
2. Episiotomy and low forceps delivery	34, 7 multipara
3. Episiotomy and spontaneous delivery	20
4. Scanzoni maneuver and episiotomy	3, all primipara
5. Kielland rotation and extraction	2
6. Manual rotation and forceps	9, one secundipara
7. Deep transverse arrest and Kielland	1, primipara
8. Manual removal of placenta for which supplementary ether was used	1
9. Cesarean section, in which subcutaneous infiltration was also used	2

Discussion of Results

In the White Memorial Obstetrical Hospital during the period covered by this series of cases (January 1 to April 27) there were 581 deliveries of which 160 or 27.5 per cent received caudal injections. The incidence of operative delivery (not including episiotomy alone) for the entire 581 cases was 19.6 per cent, while for the patients receiving caudal anesthesia the operative incidence was 36.2 per cent. From January 1, to April 27, of 1942, there were 385 deliveries with an incidence of surgical interference of 15.6 per cent. This increased incidence of operative delivery was made up largely of outlet forceps and episiotomy which in this teaching hospital has not become a routine procedure. In hospitals where most primipara are delivered by this method the operative deliveries would not be increased to any great extent.

Failure of the head to rotate necessitated operative aid in fifteen cases or 9.4 per cent. Taken month by month, the incidence of manual aid for failure to rotate has varied from 1 per cent to 4 per cent for the entire number of deliveries. This clear-cut increase in occiput posteriors is probably due to the lack of "bearing down sensation" and accompanying expulsive effort which added to the uterine contraction secures more forcible descent and subsequent rotation. Another factor is the relaxation of levator ani and perineal muscles depriving the head of the "perineal scoop" which normally insures anterior rotation of the occiput. Manual and forceps rotation is accomplished with ease in the usual case under caudal anesthesia; the muscles of the pelvis are well relaxed, facilitating the procedure, and supplementary anesthesia is seldom necessary.

Quantitative estimation of blood loss with caudal anesthesia has not been made, but the distinct impression is gained by all members of the staff observing these cases that the blood loss is less than average. Many women are delivered with but a few cubic centimeters of blood mixed with amniotic fluid following the placenta.

Observation of cases following delivery aided by caudal anesthesia reveals certain complications of varying degrees of severity. About

half of the patients complain of tenderness on pressure over the sacrum which they seldom note before palpation by the investigator. Tenderness over the sacrum occurs chiefly in cases where entry of the canal was difficult, necessitating a number of "exploratory probings" with the needle, and is probably due to this trauma plus the irritating effect of the anesthetic agent.

We have studied the report of Block and Rochberg⁶ in the use of continuous drip caudal anesthesia for obstetrics. Our experience would indicate that a certain volume must be injected in a short time to achieve sufficient height of anesthesia. Quantities less than 15 to 20 c.c. fail to ascend high enough to obliterate all pain.

Like the foregoing authors we have had one case of respiratory failure. She had been given a first injection of 30 c.c. with anesthetic level five centimeters above the navel followed by two hours of anesthesia. When her contractions again became painful, a second injection of 30 c.c. was made in fractional 10 c.c. doses with a short interval between, this precaution being taken because of the relatively high skin level of anesthesia. Within a few minutes of the last injection she complained of dizziness, faintness, and tinnitus, and became unconscious. The extern watching the patient gave artificial respiration and summoned aid which was immediately available. Blood pressure and pulse were unaltered and the patient did not become cyanotic. She was placed on the delivery table and delivered with forceps, the cervix having dilated from three centimeters to complete in the two-hour interval. It was her third child. Shortly after the delivery was completed, artificial aid to breathing became no longer necessary, having been maintained for an hour. Infant and mother were discharged from the hospital on the tenth day with no apparent ill effects. This accident was probably due to anesthesia involving upper cervical motor roots.

Occasional cases show moderate drop in blood pressure after the first administration which levels off and approaches normal. The systolic seldom goes below 80 mm. of Hg.

A few patients have complained of pains in the posterior aspect of the thighs relieved by analgesics other than opiates. We have questioned the possibility of peripheral nerve damage as the result of prolonged bathing of the nerve trunks with anesthetic agents and we are studying certain of our cases with the chronaximeter. Animal experiments are under way, using varying strengths of solutions of anesthetic agents to determine effects of prolonged action on peripheral nerves. Results of these investigations will be reported at a later date.

One primipara has imperfect bladder sphincter control. She is improving under treatment. She was delivered by Scanzoni maneuver which might well account for the difficulty.

The mental reaction of the patient toward the procedure is favorable in most cases. The usual comment is that if another baby is ever expected they will ask for caudal anesthesia. A few dislike the needle and the necessity for remaining relatively quiet.

Malleable steel needles were tried, but they seemed to offer but little advantage over the conventional steel spinal needle. Our only breakage occurred in a patient who was allowed to move about at will and on whom we used a malleable steel needle. It broke after ten hours of anesthesia but was easily recovered by pressing the skin down over the retained fragment, allowing it to come through the original perforation, and it was withdrawn with a forceps. The patient did not know of the accident.

Caudal anesthesia was used in single injection in two cesarean sections. One was a severe diabetic, and the other had an upper respiratory infection and cervical dystocia. Local skin infiltration was used in both. Peritoneal anesthesia was complete from the caudal block.

We have had no instances of fetal death or even mild degrees of asphyxia. In two instances of occiput posterior, the heart tones became irregular, but after manual rotation and forceps delivery, the infants cried immediately and lustily. This favorable result with the babies recommends the method for the premature infant.

Both metycaine, 1½ per cent in saline, and procaine, 2 per cent, were used in this series, the former constituting the majority of the cases. We are not prepared to express an opinion as to their relative merits at this time.

Summary and Conclusions

1. Certain complications are discussed, including possible peripheral nerve damage, pain in lower extremity, tenderness over sacrum, and respiratory failure.

2. There is an increase in the incidence of operative deliveries, including manual and forceps rotation for occiput posterior positions. The incidence of the latter was more than twice that of the same of previous months.

3. The procedure should be adopted with due regard for the above factors, realizing that it is no substitute for good obstetrical management.

4. For these and other reasons we suggest that adoption of the procedure by hospital staffs be preceded by intelligent planning and liaison between members of obstetric and anesthesia sections.

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THE USE OF ENDOCERVICAL AND ENDOMETRIAL SMEARS IN THE DIAGNOSIS OF CANCER AND OF OTHER CONDITIONS OF THE UTERUS

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A STUDY of the diagnostic value of vaginal smears in carcinomas of the cervix and of the fundus of the uterus has been conducted for over three years in this institution. The results of this investigation, of which a preliminary account¹ has already been presented, will be fully described in a monograph.²

The diagnosis of cancer of the uterus by vaginal smears is based on the fact that, like all the epithelial tissues of the body, the superficial cell layers of the tumor are subject to continual exfoliation. The exfoliated cells mix with the secretions of the uterus and cervix, find their way into the vagina and may be recognized in a smear of vaginal fluid.

The rate of exfoliation is variable.² Certain types of uterine cancer, like adenoma malignum, do not shed as well as others. The number of exfoliated cells depends upon the type and the developmental stage of the tumor as well as upon the existence and extent of a blood discharge. It is therefore evident that in a smear prepared from fluid obtained directly from the endocervix or from the uterine cavity, the chances of finding exfoliated cancer cells would be much greater than in corresponding smears prepared from the vaginal fluid. Of course, the vaginal smear has the advantage of being easily prepared with fluid which can be obtained without inconvenience or danger to the patient. The procurement of fluid from the uterine cavity is a more delicate procedure and one accompanied by somewhat greater technical difficulties.

The credit for demonstrating to us the practicability of the endocervical or endometrial smear belongs to Dr. George Bourgeois, of the Margaret Hague Maternity Hospital, and to Dr. William Cary, of the New York Hospital. Bourgeois used a curved metal intrauterine cannula with one terminal and several lateral apertures, as is frequently employed in tubal insufflation tests. Cary's technique, which we are now using, is described in another article in this issue. The cannula developed by Cary can be easily introduced into the endocervical canal and the uterine cavity without causing trauma or appreciable discomfort or pain to the patient. From this standpoint, it should not be compared with any endometrial aspirating curette as used in obtaining endometrial biopsies where the element of trauma is always present. The fluid of the uterine cavity is obtained by mere suction and retains its normal cytology. The technique of fixing and staining the uterine smears is the same as that used for vaginal smears.^{2, 3}

Compared to the vaginal smear, the uterine smear shows a larger number and a greater variety of endometrial and cervical cells. As a consequence, the diagnosis of cancer of the cervix as well as of the

fundus, is greatly facilitated. The irregularities and abnormalities in the structure and size of the cells and of their nuclei are more apparent in the endometrial than in the vaginal smear. Anisocytosis, nuclear gigantism, atypical fragmentation of the nuclei, even mitotic figures are encountered more frequently.

Another advantage of the endocervical or endometrial smear is that it makes possible the procurement of uterine cells, even in the absence of bleeding. In the vaginal smear, endometrial cells are usually present when there is uterine bleeding, which carries the cells into the vagina. Therefore, in the normal cycle, endometrial cells are found in the vaginal smear chiefly during the menstrual flow, whereas with an endometrial smear one can obtain endometrial cells during all stages of the cycle as well as in amenorrhea and menopause.

On the other hand, the vaginal smear presents a distinct advantage because of its simplicity and the facility with which it can be applied as a general routine method. A vaginal smear can be prepared at any time and as frequently as desired, without discomfort to the patient, and the procedure can be entrusted to a nurse or even to the patient herself. From this standpoint, we believe that it will remain as a standard routine method, whereas the endometrial smear will be applied more selectively in cases in which additional information is desired, after considering all possible contraindications, more particularly those of infection or pregnancy.

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A METHOD OF OBTAINING ENDOMETRIAL SMEARS FOR STUDY OF THEIR CELLULAR CONTENT

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THE purpose of this contribution is to describe a technique for aspirating the endometrial and/or endocervical secretions for a study of their exfoliated epithelial content, as discussed in the accompanying paper by Papanicolaou and Marehetti, and to outline the steps by which the investigation was evolved. The apparatus somewhat resembles Randall's aspirating endometrial curette with which it should not be confused, for our procedure may be carried out repeatedly with little or no discomfort to the patient and without traumatism of the tissues.

In 1929,¹ the writer presented an analysis of 266 postcoital studies performed by a standardized technique with respect to patients' preparation, hour of study and aspiration of specimens. In that paper was illustrated a cannula* devised for this technique and it was so fashioned that one end made an airtight engagement with the tip of a standard

*Since this article was written, I learn that a cannula of similar type has been employed previously in examinations of the larynx.

Luer syringe while the other end was somewhat curved and graduated in caliber to fit the cervical canal snugly and thus small portions of mucus could be gently aspirated from any part of the canal below the internal os. This cannula was made of special glass and is familiar to many gynecologists.

This study was carried out as a routine gynecologic procedure to determine both quantitatively and qualitatively the reciprocal action of the wife's secretions and the husband's semen previously evaluated by direct study. Certain observations were recorded, the significance of which was not then appreciated. For instance, it was noted that in many patients the quantity and viscosity of the cervical secretion varied at different times in the menstrual cycle, and that this secretion was most favorable for sperm cell survival and migration a few days after the cessation of menstruation. As the ovarian follicular cycle and the time of ovulation were more and more elucidated by the work of numerous investigators, it was apparent that this most favorable period evidently coincided with the preovulatory or high follicular phase. At this stage in the normally fertile woman, the uterine secretion is usually found to be more abundant, invariably alkaline (pH 7.5 or higher), transparent, mildly viscid and easily aspirated.

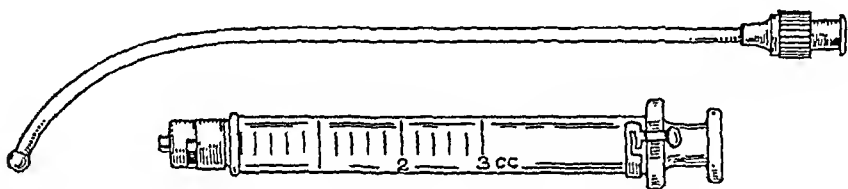


Fig. 1.—Intrauterine aspirating cannula.

The epithelial cells exfoliated from the uterine canal and almost invariably noted, singly and in groups, in smears prepared from uterine secretions were, however, wholly unappreciated as possible diagnostic criteria. It was after such smears were properly fixed and stained by the method developed for vaginal smears² that their potential diagnostic value was recognized by Papanicolaou to whom they were first submitted for a cytologic study.

In the meantime, a technique had been developed for securing fluid directly from the fundal cavity for study of the migration of spermatozoa in certain obscure cases of female infertility. Endocervical or endometrial smears and vaginal smears were prepared at specified times during the cycle, immediately fixed and submitted for investigation. Cases were selected which presented symptoms of functional deficiency and in which the likelihood of interrupting pregnancy was at a minimum.

Technique

The cannula used in securing these specimens is metal and similar in size to a uterine sound (6 F.). The overall length is 28 cm. (Fig. 1). At one end of the shaft is a broad flange within which is a thread enabling a firm union with a Luer syringe of 3 c.c. capacity, while the other, or uterine end, has a small bulbous tip. The malleability of the cannula makes it possible to shape it appropriately for introduction through any cervical canal not blocked by stenosis or extreme flexion. Endocervicitis is, of course, a contraindication to any invasion of the

uterine cavity. The cannula should be sterile and dry so that moisture in its channel will not distort the cells in the smear.

After a vaginal smear is obtained, the cervix is exposed with a speculum and any mucous wick extending from the external os is wiped away, as this is contaminated with bacteria and other vaginal elements. A simple antiseptic is applied to the surface of the cervix and the cannula introduced in the same manner as a sound. Even the discomfort of a tenaculum may be usually avoided. After introduction, the plunger of the attached syringe is withdrawn a short distance until resistance is felt and then the cannula is removed without further suction and a minimum or more of mucus can then be expelled upon a slide. This is thinly distributed and immediately fixed in alcohol and ether. The microscopic findings are reported in a separate article by Papanicolaou and Marchetti in this issue.

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57 WEST 57TH STREET

THE USE OF A PRECOITAL DOUCHE IN CASES OF INFERTILITY OF LONG DURATION*

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DURING the past fourteen months, we have observed an extended trial of a precoital douche in cases of long-standing infertility where no obvious reason for the failure to conceive was apparent. We believe that the number of conceptions presumably resulting from the use of this technique justifies a preliminary report in order that further data can be collected by a more widespread use of the method.

The use of the douche to be described was suggested as a result of studies over a period of years at Cornell Medical College on the metabolic behavior of human spermatozoa.^{1, 2} In these experiments, the spermatozoa are removed from the seminal fluid by centrifugation and transferred to a balanced salt solution containing glucose. It was found that maximal motility was maintained for many hours at 38° C. in this medium as long as an adequate supply of glucose was present. In the absence of glucose, motility failed rapidly and further investigation showed that the only foodstuff used by human spermatozoa for the production of energy for motility was glucose or any other utilizable carbohydrate (fructose, mannose, maltose and glycogen can be substituted). Furthermore, when motility failed in the absence of glucose, it could be restored maximally by the addition of glucose. In view of

*Aided by a grant from the National Committee on Maternal Health.

these facts, it was considered possible that the use of Ringer-glucose solution as a precoital douche in certain cases of infertility would be preferable to less physiological media such as bicarbonate.^{3*}

The first suggestion that Ringer-glucose solution (9 grams NaCl, 0.23 gram KCl, 0.22 gram CaCl₂, 20 grams glucose (C.P.) to 1,000 c.c. distilled water) might have value arose from a case referred to one of us (R. S. H.). The history is as follows:

Case 1.—Married six years. Contraceptives used one year. Coitus practiced very irregularly because of dyspareunia. Operation in 1937 to enlarge vaginal opening and previous unsatisfactory entrance corrected. Intercourse thereafter averaged two or three times a month in midmenstrual period. Periods regular. Husband referred for semen examination January, 1942. Excellent semen specimen, vol. 4.5 c.c., count, c.c. 263 million, motility and morphology good. Husband disclosed that wife had always used a bicarbonate douche as a lubricant just prior to intercourse.

Treatment and Result.—Ringer-glucose solution (250 c.c. to 500 c.c.) prescribed as a precoital douche to replace the bicarbonate during the fertile period. Wife conceived in first month with only one "contact." Delivered spontaneously of normal, male child.

Our reaction to this result was to consider it a coincidence. However, a similar case was presented shortly thereafter and when conception occurred in this instance almost as rapidly as in Case 1 after use of the Ringer-glucose douche, we asked several gynecologists to give the technique further trial in selected cases. The histories and results are as follows:

Case 2.—Infertility of four years' duration. No obvious defect in wife. Tubes patent, menstrual history and repeated spermigration studies normal. Vaginal smears normal which indicated ovulation between eleventh and thirteenth day of cycle. Endometrial biopsy normal. Cervical os small, dilated two and one-half years ago. Husband's specimen good, vol. 3 c.c., count, c.c. 250 million, 94 per cent normal forms and good motility. Artificial insemination with husband's semen tried eight to ten times without success. Alkaline douche used for several months without success. Ringer-glucose douche advised and conception took place in second month of trial. Spontaneous delivery of healthy male child.

Case 3.—Infertility of 2 years' duration. No obvious defect in wife. Menstrual cycle 33 to 34 days. Husband's semen specimen normal, vol. 2 c.c., count, c.c. 110 million, normal morphology and good motility. Use of Ringer's glucose douche was advised just before intercourse on the eighteenth, twentieth and twenty-second days of cycle. In first month of trial, douche used for first time on the eighteenth day and again on the twenty-second. No other intercourse during that cycle. Conception took place in this month and gestation has followed a normal course until now. Unfortunately, for a more careful control in this case, the gynecologist in charge also tried one artificial insemination using the husband's specimen on the eighth day of the same cycle.

*We have recently seen a similar statement by Rubin.⁴ "Better than sodium bicarbonate or sodium phosphate douches are the physiologic isotonic solutions, Ringer's and Locke's solutions. These are, unfortunately, better founded on theory than upon actual therapeutic experiences." From this statement, we assume that no actual experiments with these solutions were tried.

However, since the cycle in question was one of 33 to 34 days, it is unlikely that ovulation took place on the eighth day though the possibility cannot be excluded.

Case 4.—Infertility of 4 years' duration. In 1939, insufflation revealed patent tubes and menstrual history normal, 28-day cycle. Husband's specimen good, vol. 1.9 c.e., count, c.e. 120 million, good motility and morphology. In 1939, artificial insemination with husband's specimen without success. In 1940, operation disclosed small fibroid myomas and small ovarian cyst which were removed. Endometrial biopsy essentially normal with only possibility of slight corpus luteum deficiency. In 1941, couple advised to use fertile period and corpus luteum given by injection 11 days before onset of period without success. Ringer-glucose douche suggested in March, 1943, and used on the thirteenth and fifteenth days of that month's cycle. Patient did not menstruate again and a positive pregnancy test was obtained April 26.

Case 5.—Infertility of $2\frac{1}{2}$ years' duration. Gynecological examination normal in every respect. Husband's specimen good, vol. 6.5 c.e., count, c.e. 70 million with good motility and morphology. Ringer-glucose douche advised September, 1942, and conception took place January, 1943. No other therapy given.

Case 6.—Infertility of 14 months' duration. Gynecological examination normal in every respect. Husband's semen specimen rather poor, vol. 4.2 c.e., count, c.e. 17 million. Wife on thyroid therapy since July, 1942. Ringer-glucose douche advised in September, 1942, and conception took place following month.

Case 7.—Infertility of 6 years' duration. Normal gynecological examination except for thick endocervical secretion. Postcoital spermigration test negative. After Ringer-glucose douche, 30 to 40 active spermatozoa crossing h. p. f. in cervical mucus. Husband's specimen only fair, vol. 3 c.e., count, c.e. 50 million, motility good but 22 per cent abnormal forms. Advised Ringer-glucose douche and conception took place in second month of trial. Spontaneous delivery of healthy female child followed in due course.

Case 8.—Infertility of five years' duration. Twenty-six- to 29-day cycle. Severe dysmenorrhea with leucorrheal discharge for one week prior to menses. Had previous history of "injections," D and C, insufflation test and artificial insemination (husband's specimen). Latest gynecologic-abdomino-pelvic examination negative but for acutely ante-flexed uterus with cervix in axis with vagina. Repeated spermigration tests negative. Husband's semen specimen, vol. 5 c.e., count, c.e. 37 million, 35 per cent abnormal forms. No report on motility.

Treatment.—Cervical dilations monthly either on ninth, tenth or twelfth day with coitus following Ringer-glucose douche. Conception in the third month of therapy. Abortion at fourth month of gestation.

Case 9.—Infertility of 2 years' duration. Menses normal. Twenty-eight to thirty day cycle. Previous treatment for erosion of cervix. Gynecologic-abdominal-pelvic examination negative. Tubal insufflation and hysterosalpingography were normal. Repeated spermigration tests at resumed ovulation period showed no sperm in cervix. Endo-

metrial biopsy showed progestational endometrium. Husband's semen good, vol. 5 e.e., count, e.e. 163 million with normal motility and morphology.

Treatment.—Repeated cervical dilations monthly either on tenth, eleventh or twelfth days for fifteen months. Coitus during fertile period without success. Advised Ringer-glucose douche during fertile period and conception occurred in first month of trial. Delivered spontaneously of healthy male child.

Case 10.—Married nine years. Conceived and delivered spontaneously in first year of marriage. Four years of contraception followed. No conception for four years after cessation of contraception. Gynecologic-abdomino-pelvic examination and tubal insufflation normal. Sperm-migration tests negative during probable fertile period. Husband's semen good, vol. 3 e.e. count, e.e. 90 million, good motility and 18 per cent abnormal forms. Ringer-glucose douche advised and conception took place in second month of use. Healthy female child delivered.

Case 11.—Infertility of 14 months' duration. Irregular menses; 33 to 53 day cycle. Tubal insufflation showed patent tubes. Sperm-migration test revealed motile spermatozoa in cervix. Husband's semen reported as good but no details given. Ringer-glucose douche advised and it was used indiscriminately during first month of trial. No menstruation followed and patient is now in sixth month of gestation.

Case 12.—Case of artificial insemination with use of donor semen. Patient inseminated for five consecutive months on days 8 and 12, 11 and 15, 12 and 14, 10 and 14, and 9 and 13, without success. The following month, a Ringer's glucose vaginal douche was given just prior to insemination on days 12 and 14. Fertilization occurred in this month. Patient is now in seventh month of gestation.

Discussion

It might well be argued that these cases are coincidences or that other and simultaneous therapy confuses interpretation of the results. In view of the fact that many conceptions take place without therapy even after many years of infertility, it is within the bounds of possibility that several of the cases reported here would have conceived eventually. However, we believe that it is more than coincidence that, in twelve cases averaging 3.3 years of infertility, conception should take place on the average within two months (and not more than four months) after use of the douche and after all other therapy had failed. To our knowledge, the number of cases in which the douche has been used is not more than sixty. In many of these instances, the douche was begun only within the past three months so that more complete results are not available. We present these results with caution and with the emphasis that the efficacy of the technique may be restricted to the type of infertility in which both partners show no striking abnormality. On the other hand, we call attention to cases 6, 7 and 8 in which the semen specimens which produced conception were rather poor.

Lastly, in analyzing the reason for the successes listed above, it is possible that such a douche removes temporarily some incompatibility

which prevents the migration of the spermatozoa through the cervical canal. Certainly, if any douche is to be used at all, it would be advisable to use one in which the spermatozoa are known to maintain full motile activity for many hours. We added glucose to the balanced salt solution for the reason already given, namely, that glucose is the primary foodstuff from which the spermatozoa derive the energy for motility. However, it should be noted that in normal circumstances, the seminal fluid contains an abundance of this essential substance and that there should be little need for a further supply. The possible importance of a seminal pool around the external os aiding in the migration of the spermatozoa from the vagina into the cervix cannot be lightly dismissed. In this sense, any increase in the volume of this pool would be of benefit and, in view of known facts, no better diluter could be found than Ringer-glucose solution.

We are deeply indebted to Drs. S. Siegler, C. McLane, A. Greeley, H. Whiting and A. Stone (all of New York) for case histories 3 to 10.

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SKELETONIZED FETAL REMAINS

Report of Two Cases With Unusual Termination of Pregnancy

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SKELTONIZED fetal remains constitute a rare and most interesting condition. The literature on this subject is large. Much of it, however, consists of single case reports and each of these, as a rule, represents a variation of its own. Recently we have encountered two cases so remarkable in their clinical and pathologic manifestations that we have considered them worthy of report.

CASE 1.—(HIST. NO. 208208. GYN. PATH. NO. 53034.) This 22-year-old colored female was admitted to the gynecological service of the Johns Hopkins Hospital on July 28, 1941, with the complaint of lower abdominal pains. The family history was noncontributory, and the obstetrical record was the only pertinent finding in the past history. She had had three pregnancies. The first and second were four and two years prior to admission. On May 12, 1941, she was delivered at home of a premature stillborn infant. The expected date of confinement for this pregnancy was July 15, 1941. Following this delivery she had normal menstrual periods—June 8 to 15, 1941, and July 14 to 18, 1941.

Ever since the delivery of this seven months' premature stillborn infant, two and a half months before admission, she had had persistent sharp pains in the right lower quadrant of the abdomen, which gradually became worse. Two weeks before admission she had profuse leucorrhoea which abated with hot douches. There was slight nausea, but no vomiting. She believed that she had lost about 15 pounds.

On admission she was a well developed negress who was not in acute distress. Temperature 100°; pulse 98; respiration 22; and blood pressure 112/70. The general physical examination was negative. The abdomen was flat and relaxed. There was an irregular mass felt abdominally which rose to 3 to 4 fingerbreadths above the symphysis pubis. The vaginal outlet was a little relaxed and there was slight leucorrhoea. There was a moderate erosion about the cervical os. Projecting from the right border of the uterus, and intimately associated with it, was a firm nodule about 8 cm. in diameter. The adnexa were normal to palpation. The laboratory findings showed a negative serologic test for syphilis, hemoglobin 10.5 Gm., white blood count of 8,450, and urine negative.

On July 29, 1941, a total abdominal hysterectomy was done by one of us (C. P. M.). Upon opening the abdomen it was found to contain about 300 c.c. of amber, clear fluid. There was a nodule arising from the right upper portion of the uterus, which made the total uterine mass about three times its normal size. Crepitation was felt in this mass. A ball of matted loops of intestines was adherent to this mass. The adnexal organs were normal.

The uterus measures 13 by 8 by 5 cm. The surface is smooth except over the apical portion, where there is a rough, slightly raised hemorrhagic and fibrous area which measures 4 by 4 cm. There is a definite asymmetry of the uterus, a nodule arising from the right cornual area to a much higher level than the left. This nodular mass measures 7.5 by 7 by 7 cm. and the roughening noted above is over the upper surface of this mass. Upon opening the mass the myometrium is 2 to 3 cm. thick and completely surrounds a definite cavity which is 4 cm. wide. This cavity is packed with fragmented and intact bony structures representing fetal skull bones, ribs, and long bones (Fig. 1). A femur can be identified and it measures 3.7 cm. in length. Many of the bones are firmly imbedded in the myometrium which surrounds the cavity. This lining myometrium has an orange-yellow discoloration, and this material seems to infiltrate, in streaks, the adjacent myometrial wall for most of its thickness. Between this cavity and the endometrial cavity the myometrium shows less of this purulent infiltration but more scarring. At the superior border the purulent material infiltrates flush with the surface roughening. The tubal stump on the right is situated higher than the left. The mass with its thickened myometrium is about twice the size of the rest of the uterus. No gross connection between the encysted mass of bones and the uterine cavity can be made out. The cervix is 3 cm. long and measures 2.5 cm. at the external os. The area about the portio appears normal and the endocervix shows no lesion. The uterine cavity measures 7 cm. in length. The endometrium is smooth, hemorrhagic to a slight degree, and measures 2 mm. in thickness. A probe can be passed from the endometrial cavity out through the left tubal stump, but no entrance of the tube from the opposite cornual area can be found into the uterine cavity.

The section of the cervix reveals a moderate cervicitis. Sections of the uterus showing the endometrium reveal an endometrial stroma of a loose fibrous texture. There is a minimal infiltration of the stroma with small round cells, and this infiltration is almost entirely confined to the surface regions. Most of the glands are small, circular, and straight, although a few of them show early tortuosity. The glandular epithelium reveals no secretory activity. The sections of the myometrium from about the encysted fetal remnants are very interesting. The inner portions show very heavy infiltration with plasma cells, lymphocytes, and polymorphonuclears. Many large cells, suggesting decidual



Fig. 1.—Case 1. The removed uterus with the intramyometrial encysted fetal remnants. Note the inflammatory reaction about the cavity and in the myometrium at the upper border particularly. Loops of intestines were adherent at the shaggy uterine surface above the mass.

cells, are seen and also a rare giant cell of the foreign body type can be seen, particularly about the engulfed bony fragments. As the periphery is approached, there are also large collections of inflammatory cells, mostly of the chronic type. These collections have a tendency to be arranged in linear streaks. The myometrium is much thickened and there is considerable scarring and disruption of the usual architecture. Most of the inflammatory reaction in the myometrium extends towards the serosal surface, but there is slight inflammation and scarring in the myometrium towards the uterine cavity. Near the surface and about the cavity the tissue is very vascular with extensive fibroblastic reaction. By consecutive sections the right tube can be followed

from the cornual stump interstitially to the very border of the encysted mass. The muscular tissue about the tube in its interstitial portion reveals the same subacute inflammation. The tubal mucosa is normal except for slight subacute inflammation. The lumen of the tube becomes larger as the bone-containing cavity is approached. Numerous sections were taken through the myometrium between this mass of bones and the endometrium, and no area is found which could be interpreted as tube or remnant of tube.

Pathology Report.—Cervicitis, chronic; endometrium, interval, non-secreatory; myometritis, subacute; intramyometrial encysted fetal remnants.

Except for a mild and transient cystitis due to *E. coli*, the postoperative course was uneventful. She was discharged on the eighteenth postoperative day, and discharge examination revealed the vaginal vault to be well-suspended with very slight induration across the apex. Follow-up in one month and five months revealed the patient asymptomatic, the incision well healed, the vagina suspended adequately, and the pelvis free of induration and abnormal masses.

Discussion

A survey of the available literature has failed to reveal a similar case on record. The closest approximation is one of the cases reported by Smith² in 1933. He found a false intrauterine cavity containing a collapsed fetal skull in the uterus of a 29-year-old female who gave a history of leucorrhea and irregular bleeding following an induced abortion (at 4 to 4½ months), 11 years previously. This was the only known or suspected pregnancy. The picture of his gross specimen is in some respects identical with Fig. 1. Rubin² in a discussion of this case of Smith's cites a case of his in which he curetted two slender shanks of bone from a 25-year-old patient who complained of sterility and dysmenorrhea for seven years. When 18 years of age, she supposedly aborted a three months' fetus. The retention of fetal remnants and of suppurating fetuses in the uterine cavity because of missed abortions or missed deliveries is infrequent. Kelly and Cullen³ removed a uterus with a suppurating eight months' fetus one year after its delivery was expected, and in another case, four years after expected delivery.

It is difficult to interpret the findings in this case. It seems unlikely that these fetal remnants had been present for any considerable length of time, in view of the short duration of symptoms and the rather active inflammation about the bones. These bones may represent the remains of a true interstitial pregnancy occurring with the intrauterine pregnancy which later was delivered stillborn. The intrauterine pregnancy, as it developed to sufficient size, compressed and killed at twenty-two weeks the interstitial pregnancy. The soft parts of the interstitial pregnancy suppurated, leaving the cavity of fetal bones. The increase in diameter of the lumen of the interstitial portion of the right tube as it approaches the intramyometrial cavity suggests this possibility. Reports of simultaneous bilateral tubal pregnancies and of one intrauterine and one tubal pregnancy are frequent enough in the literature to suggest this explanation. The finding of decidual-like cells about the bones might mean that this pregnancy found a satisfactory nidus for implantation in an island of endometrium in this interstitial portion of the tube. Müllerian epithelial derivatives are known to be stimulated

to form decidual cells by pregnancy at any point in the tract without assuming that endometrial tissue was already present. Ash⁴ has given an excellent review of the subject of interstitial pregnancy up to 1932.

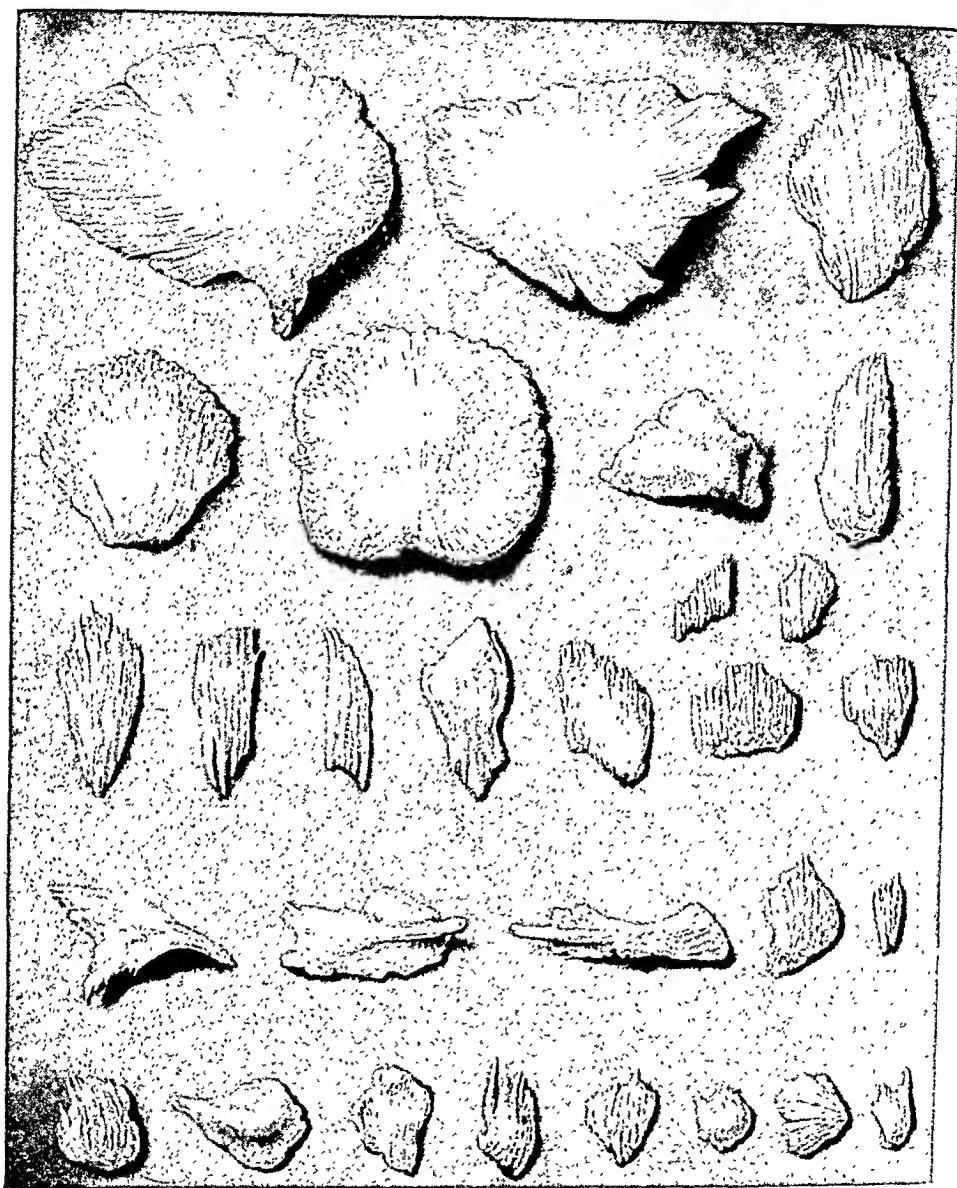


Fig. 2.—Case 2. The fragments of fetal skull bones eroding through and removed from vagina anterior to the cervix. Twice actual size.

CASE 2.—(HISTORY NO. 103324. GYN. PATH. NO. 51535 & 51639). This 21-year-old colored female was admitted to the gynecological service of the Johns Hopkins Hospital on December 1, 1940, with a complaint of left lower quadrant pain and dyspareunia. She was delivered of her first baby in 1937 by low forceps and episiotomy. Post partum she developed an ischioirectal abscess, which spontaneously opened into and drained through the vagina. No fistulous tract remained on discharge. A second fullterm delivery occurred in March,

1939, by elective low forceps and episiotomy. Since the birth of the first child a moderate leucorrhea had been present.

She was first seen in the Gynecology Dispensary on June 4, 1940. For two months she had pains in her lower abdomen and dyspareunia. Examination revealed a lacerated cervix, normal uterus, and bilateral adnexal thickening of slight degree. A diagnosis of chronic cervicitis and salpingitis was made and the patient was instructed to take douches. On July 2, 1940, she was again seen complaining of urinary frequency. The last menstrual period was May 21 to 25, 1940. A small urethral caruncle was found and the catheterized urine contained only two white blood cells per high power field. The fundus was uniformly enlarged to the size of a three months' pregnancy and the cervix was soft. She again reported on Nov. 5, 1940, with the story of an apparent miscarriage in August. During most of October she felt weak and had right flank pains radiating to the right lower quadrant of the abdomen. She did not menstruate in September, but had a profuse two weeks' period during the middle of October. On pelvic examination beneath the vaginal mucosa, anterior to the cervix, was a large piece of calcified material. The uterus was of normal size and fixed. In the left adnexal region was an adherent tender mass about 5 cm. in diameter and right adnexal region revealed thickening. Except for slight reddening about the trigone of the bladder nothing abnormal was seen through the cystoscope. A biopsy of the vaginal calcified material showed bone and chronic inflammatory tissue. She had a normal menstrual period November 14 to 17, 1940. On admission on Dec. 1, 1940, she was an asthenic Negress who did not appear acutely ill. Temperature 100.2° F.; pulse 96; respiration 24; blood pressure 130/75. The general physical examination was negative and the pelvic findings were as noted above. The impression was chronic salpingitis with tubo-ovarian inflammatory mass on the left, and possible vesical calculus eroding into the vagina. The laboratory findings showed negative serologic test for syphilis, hemoglobin 10 Gm., white blood count 11,600, urine negative microscopically, but culture revealed *E. coli*.

An instillation of methylene blue into the bladder with a sponge in the vagina showed no dye on the sponge after one-half hour. On December 5, 1940, the patient was taken to the operating room where 29 fragments of bone were removed by means of an incision in the vagina at the anterior fornix. Most of these fragments were very small, but a few of the larger fragments were identifiable as fetal skull bones (Fig. 2). The postoperative course was uneventful and the patient was sent home on the eleventh postoperative day. Laparotomy for removal of the tuboovarian mass from ruptured tubal pregnancy was not done because she was asymptomatic and because of the likelihood of spontaneous absorption. On follow-up in one year there was some induration in the anterior cul-de-sac about the vagina, but no calcified material could be felt. The uterus was normal, but a left adnexal mass extending into the posterior cul-de-sac could be felt, which was quite firm and very slightly tender. The patient was asymptomatic.

Discussion

Although it seems likely that fetal bones of a ruptured tubal pregnancy have eroded into the vagina before, we have been unable to find a report of such a case. Cullen⁵ has reported a case which was probably a secondary abdominal pregnancy following a rupture of a tubal

pregnancy that developed to eight months, and three years later a sac containing fetal bones was removed from the right lower abdomen. These bones had eroded into the bladder and into two areas of the cecum. Schewket⁶ had a case with an extrauterine fetus which 21 months later spontaneously discharged a necrotic tibia through the anterior abdominal wall. Gustafson, Meredith, and Hord⁷ reported a case in 1932 which discharged clavicle, ribs, long bones of extremities, and flat bones of the head through the rectum. There are several other reports of intestinal and bladder complications arising from the migration of fetal bones. A more frequent termination of ruptured (or unruptured) tubal pregnancy is the formation of a lithopedion. De Lee⁸ cites Wagner's case with a mummified fetus retained for 29 years. In Virchow's case the fetus retained for 28 years, and Smith reports fetus removed from a 94-year-old female 60 years after conception. Masson and Simon⁹ in 1928 reported 9 cases from the Mayo Clinic and collected 174 from the literature. In 1932 a case of an eight months' pregnancy calcified and retained for 40 years was noted by Titus and Eisaman.¹⁰ In 1935 Aschman and Helwig¹¹ reported two cases: one was a grapefruit-sized calcified mass removed from the left lower quadrant of a 69-year-old female 35 years after the last pregnancy. Hair, skull, legs and arms were identifiable. The other case was a mummified fetus weighing 546 Gm. removed from the right pelvic cavity of a 24-year-old patient fifteen months after conception.

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RHABDOMYOSARCOMA WITH ADENOCARCINOMA OF THE UTERUS

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THE occurrence of a rhabdomyosarcoma in the uterus, an organ which normally does not contain striated muscle, is extremely rare. Gunning and Ross¹ in 1940 were able to collect only ten such cases from the literature and added one of their own. The simultaneous occurrence of rhabdomyosarcoma with adenocarcinoma is even more unusual. However, the association of sarcoma with carcinoma of the uterus has been reported.²

Several theories have been expounded to explain the occurrence of rhabdomyosarcomas of the uterus. Pfannenstiel in 1892³ believed them to originate in the connective tissue of the endometrium, which later undergoes metaplasia. This is not supported by fact, for the transformation of nonstriated muscle into striated muscle has not been demonstrated. However, Nehr Korn⁴ found fully differentiated striated muscle cells in two uteri removed after puerperal sepsis. Under pathologic irritation, these could well serve as the basis for the development of rhabdomyosarcomatous tumors. Wilms in 1899⁵ believed these tumors to originate in primitive mesodermal tissue which had been carried downward during the descent of the wolffian duct. Absence of striated muscle in the wolffian body together with the development of this tumor outside the course of the wolffian duct controverts this theory. In 1907 Mönekeberg⁶ suggested that these tumors arise from cell rests in the müllerian duct. The objection to this theory is the absence of mixed mesodermal tumors in the broad ligaments despite the migration of the müllerian ducts through them. Cohnheim⁷ suggested that among the differentiated cells of almost all tissues, there are rests of very immature indifferent or embryonal cells. These are available as sources for constant replacement, for regeneration after injury and for the proliferation of tumors. The very immature anlagen of smooth muscle cells can alter their usual course of differentiation and produce striated muscle tumors. The multiplicity of theories presented make it quite evident that the exact mode of origin of these tumors is as yet obscure.

There is much confusion in the literature concerning classification of uterine sarcomas, perhaps because of the rarity of these tumors. In 1892,³ Pfannenstiel applied the name "Traubiges Sarkom" to a group of cases of sarcoma of the cervix and vagina which in the English literature have been called "botryoid sarcoma," in an attempt to describe their grapelike character. However, it must be pointed out that often they do not assume this gross appearance. In 1867, Weber⁸ introduced the concept of mesodermal mixed tumor of the uterus in the first case of its type described. Since that time Glass and Goldsmith⁹ were able to collect ninety-five cases of mixed mesodermal tumors of the uterus. However, many other types of sarcomas arising from the normal uterine constituents have been described. There may be very immature and indifferent types, the round cell, spindle cell or giant cell sarcomas, or less immature and better differentiated types, angiosarcoma, melanosarcoma, lymphosarcoma or leiomyosarcoma or mixtures of these in all possible combinations. Tumors composed of tissue which is foreign to the uterus may also occur. The case to be presented belongs to that group. It is one of rhabdomyosarcoma which, in addition, is associated with carcinoma.

Case Report

R. Z., 66-year-old German born, gravida 2, para 2, entered Mount Sinai Hospital on July 23, 1942, complaining of vaginal discharge of six months' duration associated with a 30 pound weight loss. Her past history was not pertinent to her present illness. Her present illness began six months prior to admission when she developed a vaginal discharge for which a "polyp" was removed by her physician. Symptoms persisted and another "polyp" was removed approximately ten weeks later. During this time the patient lost about 30 pounds and immediately prior to admission to the hospital, had begun to develop nausea and vomiting. Menopause had occurred seventeen years previously.

Physical examination revealed a well-developed and nourished female in no acute distress. Pelvic examination showed the cervix to be distended by a protruding neerotic mass. The uterus was irregularly enlarged to the size of a $3\frac{1}{2}$ to 4 months' gravidity. A tentative diagnosis of submucous degenerating fibroids was made with sareoma or careinoma to be excluded.

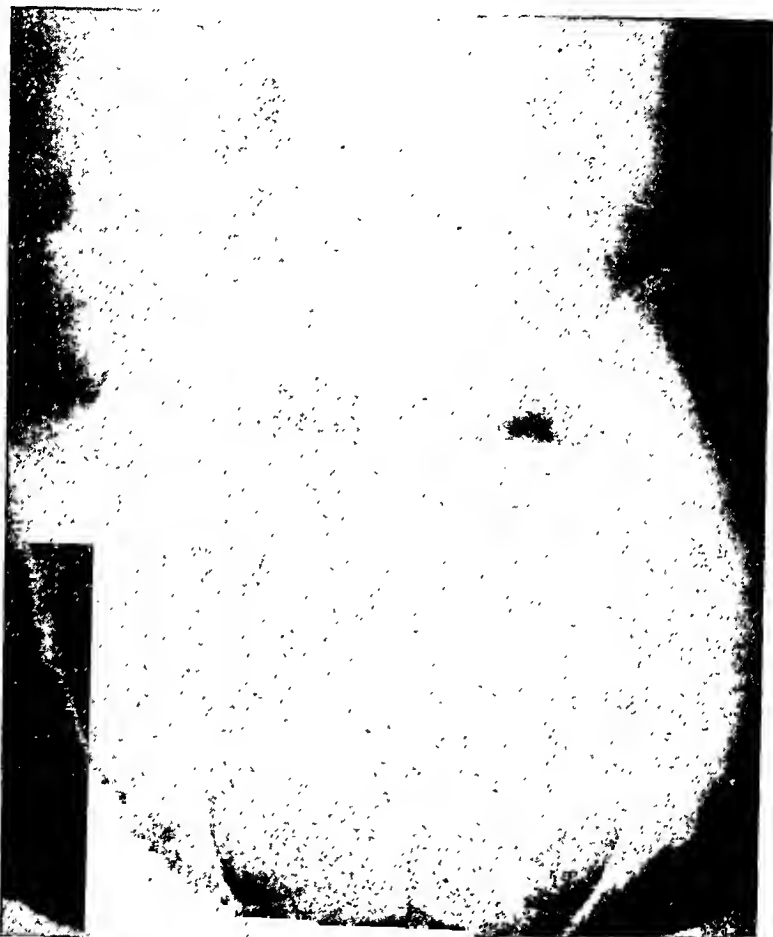


Fig. 1.—Roentgenogram showing fluid level with superimposed air in the uterine cavity.

On admission the temperature was 102° F., hemoglobin 57 per cent, white blood count 12,000, with 82 per cent polymorphonuclear leucocytes. Stools were negative for blood. Sedimentation rate over two hours. X-ray of the abdomen (Fig. 1) showed a large mass in the pelvis which extended to the level of the sacral promontory within which there was a fluid level and gas.

Temperature during the first week ranged between 99° and 103.6° F. On July 29, 1942, a vaginal hysterotomy was performed and the uterine cavity was explored. The uterus was found to contain a sessile ragged mass arising from the fundus by a broad base. Because of the extent of the mass, further surgical intervention was deemed inadvisable. A piece of tissue was removed for study. Pathological report revealed "a small fragment of adenocarcinoma with areas of marked spindle cell anaplasia." Following this procedure, the patient was treated with sulfa-

thiazole, but temperature continued to fluctuate between 99° and 103.2° F. Uterine culture taken on July 31, 1942, grew an anaerobic *streptococcus Schottmülleri* and an aerobic enterococcus. On August 8, the uterine cavity was again sounded from below. The sound was passed through the mass and struck a large loculation of pus which apparently was trapped above the tumor. The uterine cavity was irrigated with a 1% emulsion of gramaeidin. Clinically the patient improved after this procedure and temperature fluctuated between 98° and 100° F. for several days. The temperature again rose and the uterine cavity was again explored per vaginam on August 22, and another pocket of pus was opened and evacuated. The temperature again fell and uterine culture grew *streptococcus Schottmülleri*. Postoperatively the uterine cavity was irrigated through an indwelling mushroom tube and the patient was treated with sulfonamides, transfusions and deep radiotherapy in an attempt to control the local infection so as to permit surgical extirpation of the infected malignant uterus.

Despite this regime the patient's condition progressively followed a downhill course. It was finally decided that hysterectomy offered the only possibility of bringing this problem to a satisfactory solution, despite the poor condition of the patient who was confused, semi-comatose, debilitated and running a septic course. Accordingly, on September 30, 1942, after approximately two months of conservative hospital therapy, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus was symmetrically enlarged to the size of a six months' gravidity. The serosa was smooth. The uterus was soft, and its attachments to the parametria were considerably thickened by a boggy indurated process. The tubes and ovaries appeared normal. Pathological report revealed "huge necrotizing rhabdomyosarcoma of the uterus (glandular structures simulating adenocarcinoma seen in focal areas but no cartilage or other teratomatous elements found). Adnexa not involved by tumor."

Following the operation, the patient lapsed into a state of hypothermia. Her temperature remained at about 97° F. for ten days. During this period, she was given numerous transfusions. About two weeks after operation, the patient began to have swinging fever, temperature to 104° F. or 105° F. once or twice daily. She was acutely ill, semi-comatose, *in extremis*. There was left costovertebral angle tenderness and pus in the urine. Both urine and blood cultures were positive for *B. pyocyaneus*. Intravenous sulfathiazole and repeated transfusions were administered and the temperature soon fell to normal and the patient slowly recovered. Patient now responded to supportive therapy and gradually gained in strength. She was finally discharged on the sixteenth week of her hospital stay. At discharge her hemoglobin was 70 per cent, she was ambulatory and pelvic examination failed to reveal any local evidence of recurrence of the disease.

At follow-up, 7 months after operation, the patient was ambulatory, carrying on her household duties and showing no evidence of recurrence of the lesion.

Gross Pathology.—The specimen consisted of a uterus and adnexa. It was large, bulky and had a smooth serosa. When opened it measured approximately 20 cm. in length and 14 cm. across. Both tubes and ovaries appeared normal.

The entire lumen was filled by a bulky, soft, greenish, necrotic tissue which was markedly foul smelling. The tumor sprang from the uterine

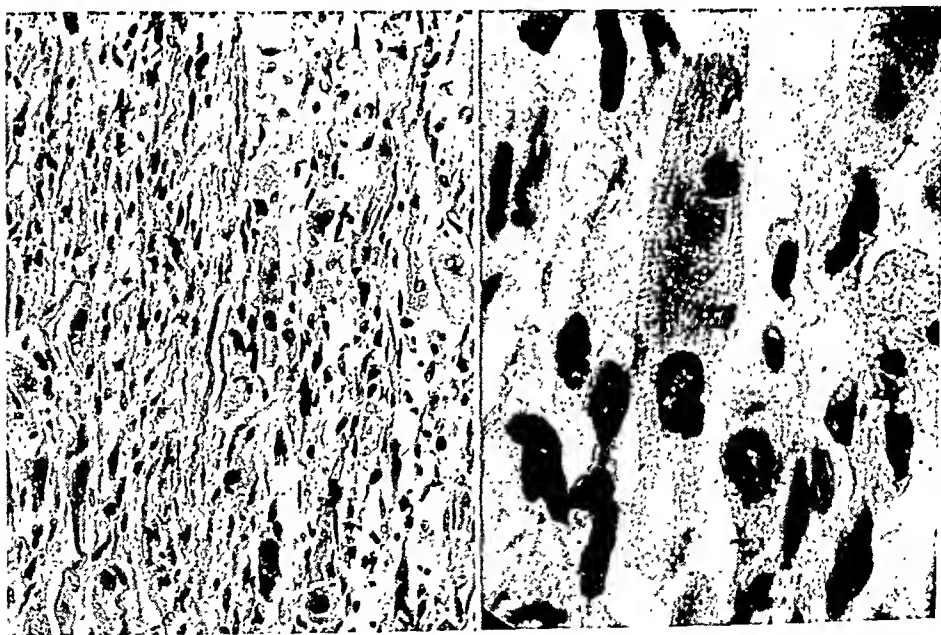
wall, but its growth was almost entirely into the lumen, the serosa remaining smooth and uninvolved. There were several small, firm nodules, approximately one-half cm. in diameter within the uterine wall. They were covered by the necrotic tumor.

Most of the tumor was necrotic and very friable. However, some of the deeper, better preserved portions showed white, smooth, cellular tissue which was fairly soft in consistency.

Microscopic Pathology.—The better preserved areas show marked cellular pleomorphism, but large elongated cells predominate. The picture is one of interlacing cells, running in all directions. There are many bulky, elongated cigar-shaped cells, others are spindle-shaped.

The cytoplasm is abundant and acidophilic in most of the cells and cross striations are frequently seen in the larger cells. The nuclei are either single or multiple and are rich in chromatin, which has a coarse granular appearance. There are many mitotic figures. Some areas reveal marked vascularity and there are many necrotic zones with leucocytic infiltrations. (Fig. 2, A and B.)

Although glandular areas characteristic of adenocarcinoma are seen, these are overshadowed by the predominant picture of rhabdomyosarcoma.



A.

B.

Fig. 2.—A, Low power photomicrograph, showing general cellular topography.
B, High power photomicrograph, showing cross striations.

Discussion

This case is extremely unusual, both because of the rarity of the pathologic lesion and the remarkable clinical course. Many microscopic sections were studied to determine the pathologic diagnosis. Of mesodermal origin, only striated muscle cells were found. On the basis of these findings, one would be justified in considering this a pure rhabdo-

myosarcoma with adenocarcinoma. Nevertheless, there is always the possibility that some unseen fragments of other types of mesodermal tissue were present but not found, since it is almost an impossibility to take serial sections of an entire uterus. Ewing¹⁰ states that the overgrowth of one element in an embryonal teratoma produces a malignant tumor of nearly uniform type, for an important principle of the growth of teratomas is the tendency of one element, either adult or embryonal, to overgrow and suppress the others.

As regards the rarity of diagnosis of rhabdomyosarcoma of the uterus, Loehrane¹¹ believes the scarcity of cases of this condition is due to the fact that special stains are necessary to detect striations, and therefore perhaps many have been missed.

Ewing and Herxheimer¹⁰ have attempted to explain the coexistence of carcinoma with sarcoma by several theories:

(a) Each tumor may develop independently of the other, at the same time, possibly as a result of the same cause acting on different tissues.

(b) Proliferation of the epithelium adjacent to a pre-existing sarcoma may occur, possibly as a result of irritation or stimulation. This may occur at the base of a pre-existing sarcoma, or at a point where a submucous or mural sarcoma meets the epithelial layer.

(c) The stroma of a carcinoma, either due to irritation, stimulation or some other cause, may undergo sarcomatous change (Herxheimer).

(d) Carcinomatous changes may occur in glands of a sarcomatous polyp.

Clinically, several points of interest may be noted. The importance of microscopic study of all tissues removed can never be overemphasized. Six months prior to admission this patient had a "polyp" removed. Perhaps had sections been studied at that time operation might have been performed much earlier. The roentgenologic appearance of a fluid level with gas in a uterus is extremely rare. Several possible modes of occurrence present themselves:

1. By mechanical introduction of air or gas into the uterus via the cervical canal and vagina. Such a case was seen by Snow¹² in which a pneumoperitoneum resulted from forceful or incorrect douching.

2. Infection due to an anaerobic gas forming organism.¹³

3. Manipulation per vaginam with a cervix that remains patulous. Negative pressure in the uterus, with the accompanying sucking in of air associated with infection may result in a fluid level with superimposed air in the uterus.

One or several of these factors may have been operating in this case.

The lack of response to chemotherapy and deep x-ray therapy is very significant.

Lastly, the necessity of surgical intervention, despite the appearance of clinical inoperability, must be stressed. The fact that this patient, in the face of all of the clinical objections to surgery, is now alive and a useful member of her family, makes it necessary to stress the importance of not considering a case inoperable until proved so at the operating table, unless there is evidence of distant metastases.

I wish to express my thanks and gratitude to Dr. Samuel H. Geist, for his aid and stimulating interest in the preparation of this work.

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FETAL DYSTOCIA DUE TO NEUROBLASTOMA OF THE ADRENALS WITH METASTASES TO THE LIVER

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ALTHOUGH a number of cases of neuroblastoma of the adrenal with metastases to the liver in newborn infants or those several days old have been reported, only two reports can be found in the literature in which dystocia was caused by the presence of the tumor mass. The case reported by Hagstrom¹ described a breech delivery in which obstructing parts were encountered at the level of the trunk of the child. Digital examination revealed the presence of a huge liver which later proved to be due to the presence of metastatic tumor masses. Portions of the liver had to be removed before delivery could be completed. Askin and Geschieker's case² was that of a full-term fetus in which the abdomen had to be incised and fragments of the enlarged liver removed before the fetus could be delivered.

The apparent rarity of the complication of dystocia of this origin prompts the following report.

Case Report

The mother of the infant was a twenty-five year-old primigravida, who was admitted to the Sinai Hospital with a history of spontaneous rupture of the membranes four hours before admission. Prenatal examination had revealed a normal bony pelvis, whose configuration was such as not to interfere with the normal delivery of an average-sized infant. The antepartum course had been completely uneventful.

After admission to the hospital, contractions of the uterus began only after stimulation with castor oil, quinine, and divided doses of pituitrin intramuscularly. Cervical dilatation progressed slowly and the head of the infant remained high in the pelvis until full dilatation, which occurred twenty-four hours after rupture of the membranes. Soon after full dilatation the head descended to the midpelvic region, but further progress ceased. Approximately one and one-half hours after full dilatation, a midforceps operation was performed and the patient was delivered of a live male child weighing 2,920 grams. No difficulty

had been encountered in delivery of the head, but hard pressure from above had been required to deliver the torso, which appeared to encounter an obstruction. The cause of the difficulty was quite evident after the delivery of the infant, since marked distention of the abdomen, apparently with fluid, was obvious. The child died one hour after delivery.

Gross Necropsy Findings.—The body was that of an apparently normally developed, full-term male child measuring 47 cm. in length. The striking feature was the protuberance of the abdomen and the bulging in both flanks. The peritoneal cavity was found to contain approximately 200 c.c. of bloody fluid. The liver was greatly enlarged and extended to both lateral borders of the abdominal wall. The right lobe extended three fingerbreadths below the costal margin in the right mid-clavicular line; the left lobe was found to extend two fingerbreadths below the costal margin in the left mid-clavicular line. The parietal peritoneum in the region of the right kidney bulged forward rather



Fig. 1.—Surface of liver showing bosselations produced by metastases.

prominently, forming an oval-shaped mass measuring approximately 10 by 8 by 5 cm. The peritoneum overlying this area had a bluish sheen. Further investigation in this area revealed a deeply hemorrhagic mass measuring 8 by 6 by 3 cm., which occupied the site of the right adrenal and extended downward over the anterior surface of the kidney. It compressed the latter but was distinctly separate from it. It was soft and palpably cystic. Upon sectioning the mass, considerable bloody fluid escaped, revealing the presence of numerous blood clots. In addition, areas of firm grayish-brown and red tissue were also visible. At the upper pole of the mass there was a thin rim of golden-yellow tissue resembling adrenal cortex. The left adrenal was found in its normal position and was relatively normal in shape but proportionately enlarged in all diameters. It measured 4 by 2 by 0.8 cm., weighed 5.8 grams, and felt nodular. The cut surface showed a well developed golden-yellow cortex, which surrounded oval-shaped nodules of grayish-white tissue averaging approximately 1.0 cm. each in diameter.



Fig. 2.—Cut surface of liver showing extensive replacement of liver parenchyma by neoplastic tissue.

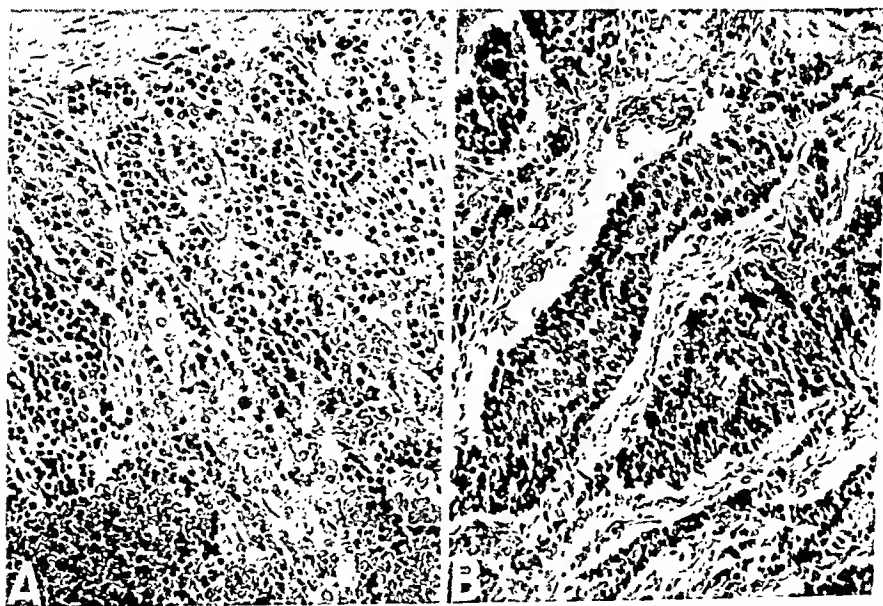


Fig. 3.—A. Section through rim of right adrenal tumor mass showing an area of intact adrenal cortex above an area of invasion by the neoplasm.
B. Section through the tumor mass in the right adrenal showing a typical area.

The liver was huge, weighed 260 grams, and measured 15 by 8 by 4.5 cm. The usual smooth, reddish-brown surface was interrupted practically everywhere by reddish and reddish-gray nodules of varying size, which produced a bosselated appearance (Fig. 1). The nodules varied in size from several millimeters to almost 2 cm. Some of the nodules showed central umbilication. The cut surfaces revealed replacement of most of the liver parenchyma by nodules of grayish-white and brown tumor tissue (Fig. 2).

The heart was normal in size and shape, and, except for the presence of a patent foramen ovale and patent ductus Botallo, was not remarkable.

The other organs showed no gross abnormalities.

Microscopic Examination.—Sections of the right adrenal tumor mass showed large areas of hemorrhage, within which, there were strands and cords of tumor cells, which were round, had a scanty eosinophilic cytoplasm and large round and oval nuclei. Scattered mitoses were seen. In some areas formations suggestive of "rosettes" were seen. The golden-yellow rim of tissue at the upper pole was found to consist of intact adrenal cortex into which scattered strands of tumor tissue were seen to infiltrate (Fig. 3). The sections of the left adrenal showed similar tumor cell masses, which occupied the medullary region, but extended into the cortex, being seen particularly in the interfascicular blood vessels of the latter.

Small nests of tumor cells were found in the interstitial and capsular tissue of the pancreas, in a lymphatic in the wall of the gall bladder, and in blood vessels in the myocardium and cerebrum.

Comment

The pathogenesis and histogenesis of the neoplastic involvement of the adrenals and liver will not be discussed, inasmuch as numerous crude presentations are already present in the literature.²⁻⁷ The probable mechanism effective in producing dystocia is, on the other hand, of pertinent interest.

Just as in the cases previously cited,¹⁻² the liver in this case was greatly enlarged. But in addition, a bloody effusion was present in the peritoneal cavity in this infant. This certainly contributed to the difficulty of passage of the fetus through the birth canal. The presence of the fluid can be accounted for on the basis of peritoneal irritation by the tumor masses present in the liver.

Although hemorrhagic degeneration in a neuroblastoma has been encountered quite frequently, it is enticing to use the presence of hemorrhage in this case to explain the rapid demise of the infant following delivery. It is possible, and even probable, that very little hemorrhagic infiltration was present in the tumor mass of the right adrenal prior to the onset of labor. This appears to be confirmed by the evident recent nature of the blood clot found in the tumor mass. Therefore, the following evolution of events is offered as being quite likely. With the onset of labor the head passed through the lower uterine segment with ease. However, when the abdomen approached this region, the muscular wall of the uterus failed to dilate sufficiently to accommodate the unusual width, thus forming a constricting band. Therefore, increased pressure was exerted upon the abdomen of the fetus. Inasmuch as the liver was huge, fluid was present in the abdomen and the ribs at this age are quite supple, the constricting force would be transmitted by the above tissues and fluid to the soft tumor mass in the right

adrenal region. Ultimately a crushing pressure would be exerted and then hemorrhage would occur into the disrupted tissue of the tumor mass. Accordingly, as the left adrenal cortex was partly invaded by tumor tissue and only little of the cortex of the right adrenal remained intact, one might blame death upon the shock concomitant with sudden interruption of a sufficient supply of adrenal cortical hormone to maintain the vis a tergo.

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RECURRENT PLACENTA PREVIA

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THE incidence of placenta previa varies from 1:150, as reported by the Committee on Prenatal Maternal Care of the White House Conference, to 1:200 to 1:1,500 as noted by various authors.¹ However, a review of the literature reveals that only nine cases of recurrent placenta previa in successive pregnancies,³⁻⁷ and one in nonsuccessive pregnancies⁸ have been reported. More cases of this type have undoubtedly been observed but not reported, for De Lee¹ and Rivett,² in discussing recurrent placenta previa, speak of a greater than reported frequency. A much larger number of cases in successive pregnancies should be expected in considering the incidence and the predisposing factors of placenta previa. However, this low incidence is apparently due to a failure to report cases and to a few principles of prophylaxis, which may also be of avail in preventing the abnormality. I desire to present another case of recurrent placenta previa in successive pregnancies.

Case Report

Mrs. A. C., aged 19, in the thirty-second week of her first pregnancy, entered the University Hospital at 9:45 P.M. on May 7, 1941, because of sudden, painless vaginal bleeding. The estimated loss of blood was 300 c.c. The prenatal period, as observed in our clinic, was within normal limits. Examination revealed a white female, who had moderate vaginal bleeding and who was not in labor. Her blood pressure was 130/80 and the pulse rate was 100. The uterus had a one-plus tone, was slightly tender in the lower segment area, and measured 28 cm. above the symphysis pubis. A single fetus lay in the L.O.P. position with a fetal heart rate of 140/minute. There was no edema present. On a lateral film of the abdomen, a 32 weeks' fetus was seen in cephalic position, but the placenta was not definitely visualized. Blood count and urine examinations were within normal limits. A diagnosis of placenta previa was made and therapy was instituted. This included blood matching and transfusion which was later followed by sterile vaginal

examination, rupture of the membranes, and application of a tight abdominal binder. Onset of labor was at 10:15 P.M., and after the loss of an additional 200 c.c. of blood, the membranes were ruptured artificially at 12:30 A.M. No placental tissue was felt at the os which was found to be dilated 3 cm. and slightly effaced. After the membranes were artificially ruptured, the fetal head descended immediately and the bleeding stopped. The patient completed a 13-hour labor, spontaneously delivering a three-pound male infant which lived. There were signs of a mild endometritis in the postpartum uterus, which was soft, boggy and tender. The placenta and fetal sac were examined by a water distension method⁹ which showed the sac to have a volume of 1,900 c.c., to be pear-shaped with bulges at the uterine horn areas, to measure 16 cm. from side to side at the widest portion and 24 cm. from the cervical tear to the fundus, and 13 cm. anteroposteriorly. The placenta was 18 by 18 cm. in size, was circular with eccentric implantation of the cord toward the apex, and covered almost all of one anterior or posterior wall. The placenta, moreover, extended downward to within 3 cm. of the cervical rent in the membranes. The diagnosis of placenta previa was further confirmed by the presence of old clotted blood on the placenta at the site of the tear in the membranes.

The patient entered the hospital with a term pregnancy eleven months after her previous delivery with a history of sudden, painless vaginal bleeding, an estimated loss of 200 c.c. of blood. She was not in labor and had no symptoms or signs of toxemia. The soft fundus uteri was 30 cm. above the symphysis pubis. The blood pressure was 130/80 and the pulse rate was 80/minute. A single floating fetus with a heart rate of 135/minute lay in the L.O.P. position. The diagnosis of placenta previa was made again. Blood matching was done, and a sterile vaginal examination failed to reveal placental tissue over the cervical os which was found to be 2 cm. dilated and uneffaced. After the membranes were ruptured, the head descended and the bleeding stopped. Labor followed shortly and a living six-pound eleven-ounce male was delivered 3 hours later. The mother had a normal puerperium. The amniotic sac was distended by 3,400 c.c. of water, and measured 28 cm. longitudinally and 18 cm. laterally. The edge of the sac opening was 1 cm. from the margin of the lowest portion of the placenta, which apparently extended nearly to the internal os. The placenta at this point was infiltrated with old blood clots. The placenta weighed 320 grams, was oval with a longitudinal diameter of 20 cm. and a lateral diameter of 15 cm. It probably lay on the anterior wall of the uterus and slightly to the left side. The cord was 40 cm. long and almost centrally inserted into the placenta. There was a white infarct, 4 cm. in diameter, which extended from the fetal to the maternal surface, and was located about one and one-half cm. above the lower edge of the placenta.

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CLINICAL EFFECTS OF THE SYNTHETIC ESTROGEN, HEXESTROL

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AT THE Philadelphia General Hospital, the gynecology department is constantly faced with the problem of securing an effective estrogenic substance with which to combat the complaints of patients following supravaginal hysterectomy and bilateral salpingo-oophorectomy. This radical procedure is often necessary in young, colored women where chronic advanced pelvic inflammatory disease forces the gynecologist to do castrating surgery, resulting in severe menopausal complaints.

An estrogenic substance to be used in this type of work has to meet certain requirements: it should have a high estrogenic activity if given orally; its action should be prolonged in order to eliminate the necessity of frequent repetition of courses of treatment; it should be nontoxic and thus not cause untoward side reactions; and finally it should be comparatively inexpensive.

It is obvious that the natural estrogens and their derivatives cannot be used for this purpose as they are too expensive and not potent enough when administered orally. We first tried stilbestrol, which has most of the prerequisites mentioned above and which is disappointing in only one way: the frequency of nausea and vomiting. In cases followed by one of us, R. C. M., the frequency of side reactions necessitated a reversion to an oral form of natural estrogen which was not sufficiently potent to control symptoms without the addition of parenteral estrogens. The patients who were somewhat neurasthenic and were warned of the side reactions of nausea and vomiting promptly developed them after the suggestion of its occurrence was made.

We then selected another synthetic estrogen,* hexestrol, for our clinical trials as this material, to judge from what is known about it, seems to come closest to our particular needs.

So far there are only three reports on clinical work with hexestrol.† Bishop,¹ and his collaborators, made comparative studies on the action of both stilbestrol and hexestrol in relation to the menopausal syndrome, atrophic conditions of the vagina, amenorrhea, dysmenorrhea and checking lactation.

*We are here using the term "synthetic estrogen" to designate substances made synthetically and not having the phenanthrene nucleus as found in natural estrogens. Thus, we are even excluding the natural estrogens when they are obtained by synthetic methods as is now usually the case.

†Two articles have appeared since this present report was prepared, each recommending approximately the same dosage we have found effective.

This work was carried out in England and recently two series on clinical trials of hexestrol have been reported in the United States. It is the purpose of this paper to present a preliminary report of the clinical effects observed in a series of cases with surgical menopause. A subsequent report will be made concerning the use of hexestrol in normal menopause and checking of lactation.

With a number of such patients available, under reasonably well controlled conditions, it was decided to undertake the evaluation of hexestrol therapy in caring for the surgically castrate woman. Seventy-four of these patients were selected for study but it was ultimately necessary to eliminate thirty-two of the group because of their poor cooperation. Wherever possible the treatment was initiated before the onset of menopausal symptoms as a more efficient symptomatic control was expected thereby. In this connection it is interesting to note that Schneider⁴ administered estrogen preoperatively to twenty-one women in whom an artificial menopause was surgically induced. Immediate reinstitution of the same dosage postoperatively resulted in maintenance of freedom from previous symptoms and in a greatly improved convalescence.

Particular attention was paid to the control of symptoms by questioning the patients relative to frequency of hot flushes, headache, nervousness, insomnia, desire for coitus, and as to any side reactions which may have been due to the drug. Four white and thirty-eight colored patients are represented among the forty-two studied. They ranged in age from eighteen to fifty-four years. The women had all been subjected to at least bilateral salpingo-oophorectomy and the majority had had either supravaginal or total hysterectomy performed. The dosage of hexestrol was varied from 2.0 to 6.0 mg. daily with an average daily dose of 3.5 mg.

An analysis of the results reveals that five patients showed no control of hot flushes at any time; four of these patients however lapsed in treatment after averaging seven weeks' treatment and the fifth had only been followed for six weeks at the time this report was prepared, and four patients had no hot flushes at all. Of the remaining thirty-three, twenty showed partial control with seven lapses in treatment, and thirteen complete control of hot flushes with no lapses in treatment. The accompanying headache was uncontrolled in twelve cases, eight lapsed in treatment and six additional cases did not have the symptom. The remaining twenty-four cases showed partial or complete control, only one of the latter lapsed in treatment. Insomnia was absent in eighteen cases and uncontrolled in seven, five lapsed in treatment. In the remaining seventeen cases it was partially (one lapsed) or completely controlled (two lapsed). Fifteen women showed no desire for coitus and the remaining twenty-seven had some or complete return of sexual desire.

At the time this study was begun February, 1941, no adequate dosage was known, and since the previous work done with the drug had shown that the largest dosage used for any length of time was 2.0 mg. daily,

we increased the dosage cautiously. Early in the work it became evident that this dose was inadequate and increases in dosage were made on the scale of 2.0 mg. daily. In four cases the dosage was elevated to 8.0 mg. daily without any appreciable change. In only one case was any side reaction noted and this only in the form of nausea, which began when the drug was instituted and continued throughout the course of treatment. No vomiting was noted at any time.

Although no concomitant series of cases was run using stilbestrol as the estrogenic substance, it is obvious that hexestrol requires heavier dosage than stilbestrol. This statement is based on previous personal experience (R C M) with stilbestrol where 1.0 mg. daily is an adequate maintenance dose. If the treatment is begun on the 6.0 mg. daily dosage of hexestrol, control of symptoms is usually secured in from eighteen to twenty weeks, these figures conform with those cases treated with stilbestrol. This factor is not eliminated but the patient is made comfortable while passing through this period.

An explanation of the final result in the cases is enlightening. In the twelve cases which spontaneously lapsed treatment, all but five were under control and none of these has returned as a recurrence. From a total of nineteen cases discharged asymptomatic, only two have returned with a recurrence of symptoms. These were immediately placed on maximum dosage and are slowly coming under control again. The cases which have been discharged without recurrence have been observed no less than four months and one case as long as ten months. Those patients who are continuing treatment are doing so because of failure to control symptoms completely or because not enough time has elapsed for effective control to make its appearance. In one case only bilateral salpingo-oophorectomy was done and the uterus was allowed to remain; under hexestrol therapy this patient maintains a regular menstrual cycle, anovulatory in type with associated hypomenorrhea.

Several patients suffering from normal menopause are now under treatment and, although the number of cases is insufficient to make an adequate comparison with the surgical menopause, we are led to believe that hexestrol will be effective in controlling this type patient. The patients already show a definite return to a more normal menstrual cycle and control of symptoms. Because of the neurotic element of the normal menopause it is apparent that the correct evaluation of control will be more difficult. The surgically castrate woman has not had the opportunity to develop this element and her control is more easily evaluated. The actual point at which it will be feasible to discharge the normal menopause case will be more difficult to determine and it is expected that recurrence will be more frequent.

Proper study of the vaginal smear, as a method of control, has not been complete in this investigation because of the inability to secure technical aid. This factor is being remedied and the complete report will appear

in a later paper where we shall also report on the value of the drug in other estrogenic deficiency states.

In view of the fact that esters of estrogenic substance often show certain advantages, especially a more prolonged and regulated action, in comparison to the unesterified mother compounds, some preliminary tests were made with hexestryl dibenzoate. This substance is oil soluble, and is reported to be less potent than hexestrol itself, Forman.³ When, in the course of this study, hexestryl dibenzoate tablets, each containing 2.54 mg. of the ester, which amount is chemically equivalent to 2 mg. hexestrol, were substituted for hexestrol tablets, no change in efficiency was observed and no untoward side reactions occurred. The trial of this substance is being continued in the study of the normal menopause cases.

Summary

1. The synthetic estrogen "hexestrol" has been given a preliminary clinical trial.

2. Hexestrol is actively potent in the control of the menopausal symptoms of the surgically castrate woman.

3. A threshold dose has been established at 6.0 mg. daily, which may be given over long periods without producing serious side reactions. Untoward side reactions are so infrequent as to be considered negligible.

4. Hexestrol having this advantage over stilbestrol and, like stilbestrol, being much cheaper than the natural estrogens, and effective when administered orally, it should be submitted to further extensive clinical tests of its value in the treatment of the normal menopause.

The hexestrol preparations used in this study were generously supplied by Jovan Laboratories, Inc., New York, N. Y.

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VULVOVAGINAL MYCOSIS

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THE presence of fungi in the mucous membrane lined cavities of the body has been determined by Benham and Hopkins¹ and Todd.⁵ The disturbances produced by pathogenic fungi in the vagina have been studied by Plass and his co-workers⁶ and Hesselstine.²⁻⁴

The symptoms and signs of mycotic vulvovaginitis vary considerably. The usual complaints are itching and burning of the vulva and vagina, and burning on urination, with or without vaginal discharge. Characteristically the itching is worse during the premenstrual period. The clinical picture has been described in detail by Minnich⁵ and Plass.^{6, 7}

The diagnosis should be made by combined clinical and bacteriologic examinations. Bacteriologic findings in a series of one hundred private patients examined routinely during the last trimester of pregnancy are shown in Table I.

TABLE I

1. PATIENTS NOT VOLUNTARILY COMPLAINING OF VAGINAL AND/OR URETHRAL DISCHARGE OR IRRITATION		96
Monilia	5	
Trichomonas	8	
Monilia and Trichomonas	2	
2. PATIENTS VOLUNTARILY COMPLAINING OF VAGINAL AND/OR URETHRAL DISCHARGE OR IRRITATION		4
Monilia	2	
Trichomonas	1	
Monilia and Trichomonas	1	

One hundred twenty-eight nonpregnant patients complaining of vaginal and/or vulval discharge or irritation were studied in a similar manner with results as indicated in Table II.

TABLE II

1. Monilia	25
2. Trichomonas	97
3. Monilia and Trichomonas	6

The treatment of vulvovaginal mycosis has not been entirely satisfactory in the past. Many agents have been used, the most common one being gentian violet, one or two per cent, in aqueous or alcoholic solution, combined with alkaline douches. This treatment not only gives unsatisfactory results but is unpleasant for both patient and physician. Gentian violet in alcoholic solution gives better results than when in aqueous solution, but in addition to being painful, violent tissue reactions occasionally are encountered in sensitive patients.

Dissatisfied with this form of treatment, Minnich⁵ advocated the following preparation:

Thymol	0.2 per cent
Sodium lauryl sulfonate	3.0 per cent
Eucalyptol	0.1 per cent
Menthol	0.1 per cent
Oil of Wintergreen	0.1 per cent
Sodium perborate	q.s.

The essential ingredients of the powder are thymol, sodium lauryl sulfonate and sodium perborate. It is evident that the percentage of thymol is smaller than one would think necessary to prove fungicidal. However, the action of this drug seems to be enhanced by the other materials contained in the powder, especially sodium perborate. Lowering of surface tension by sodium lauryl sulfonate also plays an important part in producing fungicidal activity. The role of the aromatic oils has not been adequately studied, but it is possible that any or all of these might be eliminated from the formula except for their pleasant odor.

The thymol content of the mixture can be varied if necessary to suit the sensitivity of the patient. However, Minnich⁵ points out that if the thymol content is more than 0.5 per cent, tissue reactions similar to those produced by gentian violet in alcoholic solution may be induced.

He suggests cleansing both vagina and vulva, with particular attention to the clitoris, using a ten per cent solution of the powder (one heaping tablespoon to ten ounces of water). This is followed by daily douches using one tablespoon of the powder to one quart of water. Complete relief of symptoms was obtained in fifteen patients treated by this method, the average duration of treatment being from two to three weeks. Two successive negative weekly cultures were suggested as a criterion for cure.

The author has treated eighteen private patients with vaginal and/or vulval irritation, using the powder suggested by Minnich.⁵ All had positive cultures on Sabouraud's medium. All were relatively acute with the exception of two, one of whom had symptoms of eight months' duration, and the other of one year's duration. In both the latter there were marked skin changes resembling chronic atrophic vulvitis, and both had been treated with most of the preparations commonly employed in the management of trichomonas vaginitis. In both, the principal symptom was pruritus vulvae and ani, and roentgen therapy had been given without relief. One patient had a combined infection, with a mycotic vulvitis and a trichomonas vaginitis.

Therapy in the entire group of patients consisted of biweekly or tri-weekly office treatments depending on the severity of the symptoms. Using cotton balls soaked in a ten per cent solution of the powder (one heaping tablespoon of powder to ten ounces of water), the vagina, vulva, clitoris and anal region were cleansed thoroughly. The vagina

was irrigated with the solution, using a vaginal syringe. The patients were also instructed to cleanse these areas twice daily at home with the more dilute solution (one heaping tablespoon of powder to one quart of water), and to use the remainder as a douche after each cleansing. They were cautioned to make sure that the powder was dissolved, and were instructed not to wear pads. Fifteen patients were treated for two weeks, after which time the vulva and vagina appeared normal and symptoms had subsided. Cultures of the secretions of vagina and vulva on Sabouraud's medium were negative for two successive weeks. In the patient with a combined trichomonas and mycotic infection, the vulvitis was treated first and with results similar to those in the above group. Following this, the trichomonas infection was eradicated by suitable measures. The two patients with symptoms of several months' duration were treated in a similar manner, with gradual decrease in frequency of office visits, until all symptoms had cleared, and the appearance of the vulva was normal. At the end of two months, two negative cultures were obtained at weekly intervals. In one of the patients, itching about the vulva persisted until relieved by injection with ninety-five per cent alcohol.

Discussion

An attempt has been made to verify the effectiveness of a treatment for mycotic vulvovaginitis originally described by Minnich. Results were excellent, clinical and bacteriologic proof of cure being obtained in every instance. In spite of the relatively small number of patients included in both series, the uniform success obtained suggests that this procedure should be employed more often. Those individuals who see more than an occasional case of mycotic vulvovaginitis will welcome its simplicity and effectiveness. Individual cases generally will respond to the older methods of treatment, but use of the preparation described above will increase the likelihood of cure and will obviate the undesirable features associated with gentian violet. It is probable that this treatment will prove equally efficacious in the hands of the patient without the necessity of office therapy.

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Department of Statistics

VAGINAL HYSTERECTOMY

Analysis of 305 Consecutive Cases

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DURING the ten-year period from Jan. 1, 1931, to Jan. 1, 1942, one of us (C. H. T.) has performed 582 consecutive abdominal hysterectomies and 305 consecutive vaginal hysterectomies. This study consists of the 305 consecutive patients upon whom a vaginal hysterectomy was performed at Touro Infirmary and Charity Hospital in New Orleans during this ten-year period. Of the entire series of 305 cases, 138 were Touro and 167 Charity Hospital cases. Most of these patients were white; only 10 in the series were Negroes. This definite preponderance of white women can be explained by the fact that the service at Charity Hospital was chiefly white, and that the vaginal approach is used much less frequently in Negroes than the abdominal. The reason for this is that in Negroes obstetric injuries as a rule are not as numerous, the fibroids are usually larger and the incidence of pelvic infections is greater.

The average age for this series was 44.8 years. Table I shows the distribution. The youngest patient was 27, the oldest 74. The greatest number of operations (171) was performed upon patients between the ages of 35 and 50. Although it is most undesirable to perform hysterectomy on women younger than 35, the age of the patient should not be an absolute contraindication in the presence of extensive prolapse and numerous complaints. Seventeen patients were 65 years or older. Here again, when hysterectomy is advisable, the age of the patient need not be weighed too heavily. The ease of the operation, the low morbidity, and the rapidity with which it can be performed, make vaginal hysterectomy the method of choice for such patients. Most of the cases fall in the age group in which obstetric injuries, complicated by menstrual disorders, abnormal vaginal discharges, and cervical carcinomas are the highest. It is this group of patients that form the greater part of gynecologic practice.

In regard to parity and gravidity, it was found that the greatest number of cases occurred in the group between the ages of 35 to 44, and the frequency in decades diminished as the age increased. Twenty-three patients were pregnant more than

TABLE I. AGE DISTRIBUTION

AGE	CASES	AGE	CASES
27-29	2	50-54	34
30-34	36	55-59	21
35-39	68	60-64	14
40-44	58	65-69	14
45-49	55	70-74	3

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TABLE II. CHIEF COMPLAINT

COMPLAINT	TOURO	CHARITY	TOTAL
Increased vaginal bleeding (irregularity also includes postmenopausal, menorrhagia, clots)	74	75	149
Bearing-down sensation (includes sensation of pressure in pelvis)	48	53	101
Lower abdominal pain	15	56	71
Backache	25	41	66
"Falling of womb"	34	20	54
Vaginal discharge	17	7	24
Bladder trouble (includes frequency and incontinence)	16	7	23
Flooding	5	5	10
Dysmenorrhea (including cramps)	6	3	9
Tumors of womb (carcinoma, "swollen womb")	1	2	3
Lacerations	0	2	2

ten times and 9 had never been pregnant. The average parity of the remainder was 2.8. The maximum parity was 19, and the maximum number of children of any one patient was 14. Of the 31 patients more than 59 years of age on whom hysterectomy was performed, 20 had 4 or more pregnancies, and 11 had less than 3. These 11 cases represent 20 per cent of the patients with a chief complaint of "falling of the womb." In most of the patients 60 or more years of age, hysterectomy was performed because of procidentia. This would suggest that previous pregnancies were not a great factor in the pathogenesis of this condition. In fact, 5 women had never been pregnant!

The chief complaints of the entire series of patients are listed in Table II. Almost one-half of the patients had menstrual abnormalities. Flooding is listed separately because it indicates urgency and was usually the sole complaint. It is also interesting to note that "lacerations" and "tumors" were limited to 5 cases, yet two-thirds of the entire series had extensive cervical disease; 7 patients had complete perineal tears (which were repaired at the time of operation) and uterine fibroids were found in 64. Vaginal discharge, other than bloody, was listed as a chief complaint in 24 cases, whereas nearly all admitted an abnormal discharge upon questioning. Of the 228 women with a history of urinary incontinence on coughing, laughing, or straining, only 23 were sufficiently disturbed by such an event to make it a specific complaint. Two-thirds of the cases had pain or a bearing-down sensation, or both, of such severity as to include this symptom as a chief complaint.

TABLE III. GYNECOLOGIC SYMPTOMS

SYMPTOMS	TOURO	CHARITY	TOTAL
Leucorrhea	131	165	296
Pelvic pain	124	162	286
Backache	125	147	272
Urinary symptoms:			
Frequency	119	155	274
Incontinence	96	132	228
Burning	35	63	98
Pain	30	42	72
Constipation	58	92	150
Menstrual abnormality:			
Menorrhagia	72	115	187
Clots	35	97	132
Metrorrhagia	39	59	98
Dysmenorrhea	26	48	74
Postmenopausal bleeding	36	19	55

TABLE IV. FINDINGS ON EXAMINATION

FINDINGS	TOURO	CHARITY	TOTAL
Cystocele	127	166	293
Rectocele	122	158	280
Chronic cervicitis	129	150	279
Lacerated cervix	87	152	239
Size of uterus:			
Normal	22	5	27
Slightly enlarged	8	8	16
Enlarged	88	132	220
Small	17	3	20
Prolapse of uterus:			
1 degree	39	38	77
2 degrees	51	104	155
3 degrees (procidentia)	43	25	68
Uterine fibroids	35	27	62
Retroversion of uterus	20	21	41
Stricture of cervix	15	9	24
Amputated cervix	5	3	8
Complete tears	1	6	7
Salpingitis:			
Right	0	4	4
Left	0	4	4
Bilateral	0	1	1
Endometriosis	1	2	3
Cystic ovaries	2	1	3
Abdominal mass	0	2	2
Leucoplakia of cervix	0	1	1
Residual urine	0	1	1
Pyometria	0	1	1
Hemorrhoids	1	1	2

The entire list of gynecologic symptoms is given in Table III. It is apparent that a large percentage of these patients were troubled by numerous complaints. Unfortunately, gynecologic pain and menstrual abnormalities overlap considerably so that rigid analysis cannot be made. Likewise, all complaints are included with regard to severity. Whereas 9 patients had dysmenorrhea sufficiently to complain of it primarily, 74 listed dysmenorrhea when questioned. Burning on urination is differentiated from "pain on urination"; the latter refers to vesical tenesmus, whereas the former refers to the "scalding" that chronic cystitis so frequently causes. Almost 50 per cent of these women were constipated! Fifty-five patients had bloody vaginal discharges and frank uterine postmenopausal hemorrhages, whereas there were 88 patients in whom the menopause had been passed without menstrual abnormality. As one would expect, extensive relaxation of the vaginal outlet resulting in cystoceles and rectoceles was found in 95 per cent and 91 per cent of the series, respectively. The incidence of chronic cervicitis was lower probably because of the atrophy found in cases at or beyond the menopause. In 20 cases the uterus was noted as "small" or atrophic. Palpable enlargement of the organ is not a contraindication for the procedure, since enlargement was noted in 77 per cent of this series. Other findings of particular interest are stricture of the cervix due to previous surgical procedures in 24 cases, complete tears of the perineum in 7, and endometriosis in 3.

Medical complications (Table V) occurred in 74 cases, the most frequent of which was hypertension. Diabetes was present in 4, and was responsible for one of the fatalities. A previous surgical procedure was performed 143 times (Table VI), and 74 patients had had previous lower abdominal operations. Although a lower abdominal scar is a natural deterrent when considering the advisability of the vaginal approach, it need not be held as an absolute contraindication. It should also

be noted that suspension of the uterus was performed in 15, and the interposition operation in 2 cases. At this later date, the advisability of temporizing in these women might be questioned. There is no doubt that the subsequent operation was made more difficult as a result.

TABLE V. MEDICAL COMPLICATIONS

COMPLICATIONS	TOURO	CHARITY	TOTAL
Hypertension (150/90 or over)	33	26	59
Hypotension (less than 100/60)	1	1	2
Other heart disease	0	2	2
Positive Wassermann	0	5	5
Diabetes	1	3	4
Severe anemia	0	1	1
Tuberculosis	1	0	1
Total	36	38	74

TABLE VI. PREVIOUS SURGICAL PROCEDURES

SURGICAL PROCEDURE	TOURO	CHARITY	TOTAL
Cervical:			
Plastic (Including amputation, con- ization and dilatation and curettage)	28	15	43
Radium	4	3	7
Perineorrhaphy	11	7	18
Appendectomy	21	12	33
Suspension of uterus	11	4	15
Salpingectomy:			
Right	4	1	5
Left	1	0	1
Bilateral	1	2	3
Oophorectomy (right)	4	0	4
Hernioplasty (umbilical)	1	2	3
Interposition	2	0	2
Ligation of tubes	0	1	1
"Pelvic operation"	0	1	1
Hemorrhoidectomy	0	1	1
Repair of complete tear	0	1	1
Kidney operation	0	1	1
Thyroidectomy	0	1	1
Cesarean section	0	1	1
"Gall bladder"	0	1	1
Pneumolysis	1	0	1
Total	89	54	143

Eighty-seven per cent of the patients had a maximum temperature of 101° F. or less, and 48 per cent, 100° F. The greatest cause of postoperative fever (Table VII) was urinary in origin, and this occurred in 21 per cent of all cases. Before the advent of the sulfonamide drugs, indwelling catheters, lavage, and urotropin were used to control urinary infection. More recently, extensive local manipulations have been reduced to a minimum by the administration of sulfanilamide and sulfathiazole in full therapeutic doses. The use of these drugs has definitely reduced the incidence of postoperative morbidity. An indwelling catheter has been employed in cases in which urinary retention is a complicating factor, but its use is avoided whenever possible. Postoperative bleeding required packing in 4 instances. Peritonitis was clinically diagnosed in 3 patients, one of whom died. Auricular fibrillation occurred but was controlled without ill effect in one case. As in any series of extensive plastic procedures, bladder injuries were sustained by two patients, in one of whom im-

mediate repair was successful. Later, however, the other patient returned, and the vesicovaginal fistula was successfully closed. Severe postoperative shock occurred in one case, resulting in pronounced atelectasis and death. The mortality rate for this series was 0.65 per cent.

Eighty-one per cent of the patients were in the hospital fourteen days or less with the shortest stay eight, and the longest forty-five days. The average hospital stay for the Touro cases was 12.4 days and for the Charity Hospital group fourteen days.

TABLE VII. COMPLICATIONS

COMPLICATION	TOURO	CHARITY	TOTAL
Cystitis (pyelitis, pus in urine)	39	27	66
Pelvic abscess	1	3	4
Postoperative pelvic bleeding	2	2	4
Wound infection	1	2	3
Peritonitis	1	2	3
Deaths	0	2	2
Auricular fibrillation	1	0	1
Cellulitis of buttocks	1	0	1
Bladder injury repaired (no fistula)	1	0	1
Postoperative vesicovaginal fistula	1	0	1
Parotitis	0	1	1
(Transfusion, preoperative)	0	7	7
(Transfusion, postoperative)	0	8	8
Fatal postoperative shock	0	1	1

TABLE VIII. OPERATIVE PROCEDURES IN ADDITION TO VAGINAL HYSTERECTOMY AND PERINEORRHAPHY

PROCEDURE	TOURO	CHARITY	TOTAL
Repair of complete tear	1	6	7
Salpingectomy:			
Right	0	4	4
Left	1	3	4
Bilateral	3	1	4
Hemorrhoidectomy	3	0	3
Bladder opened	0	2	2
Appendectomy	2	0	2

The entire series of patients had much the same preoperative preparation. A large percentage required no particular preparation other than preoperative cleansing douches and sedation. If proidentia was complicated by cervical erosions and ulcerations, bed rest and daily cleansing douches were employed until the ulcerations had clinically improved. It is felt that the cervical lesions increased the frequency of postoperative infections of the peritoneum, wound, and bladder. In an effort to reduce vaginal flora to a minimum, aqueous merthiolate was instilled following preoperative douches. This caused neither irritation nor annoyance to the patient. If polyps or submucous fibroids were protruding through the cervix, these were removed at least two weeks prior to the vaginal hysterectomy. Opening the peritoneum in the presence of infected polyps or degenerating fibroids increases the frequency of postoperative pelvic inflammation.

In all cases with medical complications, such as hypertension, tuberculosis, and diabetes, medical consultations were requested to prevent complications. One death in this series might have been avoided had the diabetic state of the patient been recognized prior to operation. In the presence of severe anemia, preoperative transfusion was given.

An inhalation anesthetic, either ether or gas, alone or combined, was preferred. A spinal anesthetic was employed if inhalation was contraindicated, but a local

anesthetic was used on one occasion in an elderly patient. It is a remarkable coincidence that pneumonia did not occur as a complication, although severe atelectasis did develop with unfortunate consequences in the one case of severe postoperative shock.

There were slight modifications in the technique of vaginal hysterectomy used in this series. Following preliminary preparation of the vagina, a circular incision was made through the mucous membrane around the cervix. From this an incision was then made in the midline to within 2 cm. of the external urethra. The vaginal mucous membrane was reflected laterally, the bladder displaced upward, and the vesicouterine peritoneal fold incised transversely. The pelvis was explored digitally through the opening in the peritoneum. The anterior wall of the uterus was grasped with the tenaculum and delivered into the vagina. At this stage, in cases of fibroids if it was necessary to reduce the uterine mass, myomectomy was performed. The broad ligament structures were clamped, excised, and ligated separately. These structures were brought together separately in the midline and the upper portion of the broad ligament structures including the round ligaments was sutured to the pubovesical fascia. The base of the broad ligaments was sutured together in the midline and the cul-de-sac eliminated. The vesicovaginal fascia was then sutured together in the midline to the united stump of the broad ligament structures. Interrupted sutures of chromic No. 1 were used throughout.

TABLE IX. MICROSCOPIC PATHOLOGY

PATHOLOGY	TOURO	CHARITY	TOTAL
Chronic cervicitis (including erosion, ulceration)	137	0*	137
Leiomyoma	38	26	64
Endometriosis of uterus	11	0	11
Carcinoma of cervix	7	2	9
Chronic salpingitis	0	6	6
Adenocarcinoma of fundus	0	1	1
Adenomyoma	1	2	3
Cystic ovaries	0	2	2
Sarcoma (leiomyosarcoma)	1	0	1
Cystadenoma of ovary	1	0	1
Angiofibroma of cervix	0	1	1

*Not reported.

Perineorrhaphy was performed in practically every case. Additional procedures were performed as required (Table VIII). The duration of operation varied from twenty to eighty minutes, with an average of 47.7 minutes for the Charity group and 43.7 minutes for the Touro patients. The average time has been found to be shorter for cases of complete procidentia than for cases of incomplete prolapse. This fact has broadened the indications for surgical intervention in the elderly female, since it is felt that the frequency of complications generally is directly proportional to the duration of the operation.

The various pathologic conditions reported are enumerated in Table IX. Chronic cervicitis was the most common condition reported by the pathologist. In 10 cases the malignant condition of the uterus was so early that it could only be detected by the pathologist. It is interesting to note that endometriosis was found in 11 of the cases at Touro Infirmary, whereas this condition was not reported in any case at Charity Hospital.

Summary

A detailed analysis of 305 consecutive cases of vaginal hysterectomy with a mortality rate of 0.65 per cent is presented.

Department of Reviews and Abstracts

Selected Abstracts

THE INFLUENCE OF THE HORMONAL STEROIDS ON URINARY TRACT DISTURBANCES ASSOCIATED WITH GYNECOLOGIC DISORDERS

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THERE have been many recent reports on the clinical effects of the steroid hormones on urinary tract disturbances, especially those associated with gynecologic disorders. This led me to review the effect of the hormonal steroids on the urinary system and to consider the therapeutic uses for, and the dangers in the use of the steroid hormones in urinary tract disturbances associated with gynecologic disorders. The steroid hormones considered are the androgens, the ovarian hormones and desoxycorticosterone acetate.

Differences in kidney structure in the two sexes have been noted. A larger kidney was found in the male than the female guinea pig,¹⁻² mouse³ and rat.⁴ Crabtree⁵ and Selye,⁶ demonstrated that in mice there is a sexual difference in type of Bowman's capsule as well as weight of the kidney. In amphibia there are two types of Malpighian corpuscle in the kidney,⁷ of which one is sexual.⁸ Rugh⁹ reported that he was able to trace the course of spermatozoa through the kidney in the male frog, *Rana pipiens*.

Gonadectomy in male animals has been noted to influence the renal structure. Kidney size and weight decreased after testis extirpation in guinea pigs,¹ mice⁵ and rats.¹⁰⁻¹³ After gonadectomy the kidney size of males decreased much more than that of females, and the kidney weights approximated each other.^{2, 14} After the castration of male mice the Bowman's capsule changed to the female type and the renal weight decreased.^{5, 14} Crabtree⁵ noted that there was also a regeneration of the x-zone or androgenic zone of the adrenal after castration of male mice.

Selye¹⁵ believes that testosterone has a normal physiologic effect on the kidney. The renotropic action of the androgens in the intact animal was noted by Ludden and Kruger¹⁶ and others. Treatment with testosterone propionate was followed by hypertrophy of the "sexual segment" in the kidney of the chameleon (*Anolis carolinensis*).¹⁷ It was demonstrated that treatment with testosterone or its propionate caused marked enlargement of the whole mouse kidney, exaggerated the male characteristic of the kidney in the males and changed the female kidney into the male type.^{5, 18} Histologically, these kidneys were characterized by pronounced hypertrophy of the epithelium of the convoluted tubules and of the epithelial lining of the parietal lamina of Bowman's capsule.⁶ Pfeiffer, et al.,¹⁹ noted increased renal weights in young male mice with testosterone and its propionate, and found the latter more active. Testosterone or testosterone propionate caused enlargement of the kidney in the male and female rat also.²⁰ However, the effect was not as marked as in the mouse and was not accompanied by changes in Bowman's capsule. Moreover, testosterone propionate prevented the renal weight decrease action of estradiol.

Korenchevsky and Ross¹⁰ noted the same results and were the first to use the term "nephrotrophic" to describe this androgenic kidney stimulating effect. In immature rats testosterone propionate was also found to produce renal hypertrophy that persisted for a considerable length of time after treatment was discontinued.²¹ Ludden, et al.²² demonstrated that a definite significant increase was produced in the renal weight of male and female rats when testosterone propionate was used. They noted that there was a greater effect in males than in females, and that testosterone propionate appeared to have the most marked effect. When the optimal dose of testosterone propionate was reached, an additional amount produced no further renal enlargement. However, the simultaneous administration of one of the other steroids mentioned produced additional enlargement by an additive effect. They, too, found hypertrophy and perhaps hyperplasia of the convoluted tubules.

The findings in gonadectomized animals treated with the androgens have followed a similar pattern. Renal weight increases in castrated male rats were reported following the administration of androgens.¹⁰⁻¹³ Korenchevsky and Ross¹⁰ and Selye³ described hypertrophy of the kidneys in ovariectomized mice even above that of normal males following the use of androgens. Others²³ reported restoration of the atrophic kidney of the castrated male to or towards normal by the use of androgens. Testosterone restored the sexual characteristics of Bowman's capsule in castrated male mice.¹⁴ Crabtree⁵ compared the findings in male mice after castration with those after castration and treatment with testosterone propionate. She found that the kidney weight which had decreased, increased with hypertrophy of all parts; that Bowman's capsule, which had changed to the female type, returned to the male type; and that the x-zone or androgenic zone of the adrenal, which had regenerated, returned to its former status. Deansely²⁴ found that in young pregnant mice premature degeneration of the androgenic zone of the adrenal accompanied the alteration in amounts and types of endocrines secreted.

It has been inferred by some and shown by others that the increase in parenchymatous renal tissue by the androgens may favorably influence renal function. Testosterone caused an increase in renal tubule activity.²⁵ Diodrast excretion increased as much as 100 per cent after testosterone propionate was given to female dogs. However, neither the glomerular filtration rate nor the renal blood flow was significantly affected. Selye¹⁴ and Longley⁷³ showed that testosterone exerted a protective influence against the kidney damaging effect of sublimate. Others²³ noted that the androgens were able to restore the atrophic kidney to or towards normal. Moreover, renal atrophy, which usually develops subsequent to the hydronephrosis caused by unilateral ligation of the ureter, may be inhibited or delayed by testosterone administration.²⁶ Testosterone propionate considerably increased the compensatory renal hypertrophy following unilateral nephrectomy. Selye²⁰ believes that the kidneys of testosterone treated animals are "functionally superior" to those of non-treated animals in that they are more resistant to nephrotoxic agents. Furthermore, the actions of testosterone esters appear to have no harmful effect on the kidneys except for some pathologic changes in the kidneys of normal rats after very large doses.¹⁰

The findings on the effect of ovariectomy on kidney structure have shown some variations. The kidneys of ovariectomized guinea pigs¹ and mice^{2, 27} were only slightly smaller than those of intact animals. Selye³ found that there was no marked weight decrease in the mouse kidney following ovariectomy. Another group²⁸ saw slight deviations from the normal after ovariectomy in short term experiments. They found, however, that the development of the kidneys became quite subnormal sixty days after spaying. Others found that the size of the kidneys of males decreased much more markedly than that of females after gonadectomy and that the kidney weights approximated each other.^{2, 14, 27}

The results have been variable on the effect of ovarian hormones on the kidney structure of intact animals. One of the earliest workers, Iscovesco,²⁹ used an estrogenic lipid extract of the ovaries and did not notice any change in the size of the kidney. Recently the same results were observed after estradiol benzoate was used in male and female rats.³⁰ In his earlier work Selye^{20, 37} showed that continued therapy with estradiol or diethylstilbestrol caused a marked decrease in kidney weight in the male and female rat. The effect could be counteracted by testosterone propionate, desoxycorticosterone acetate, or progesterone. However, in spite of continued therapy the weight returned to normal limits after a certain time. His later work³¹ showed that estrogens occasionally caused an increase in kidney size. This was always transitory and merely the result of edema. Pfeiffer, et al.¹⁹ demonstrated increased renal weights in young male mice with estradiol benzoate and dipropionate. Others^{10, 22} found that estradiol benzoate, when administered in effective doses, produced a significant increase in renal weights of male and female rats, being greater in the former. The change was produced by the retention of edema fluid in the renal tissues causing the enlargement and increased weight. Progesterone also caused a marked increase in renal weight in male and female rats and mice.^{20, 37} Neither the progesterone nor the estrogens influenced the development of the renal lesions which were produced by the partial occlusion of the aorta proximal to the renal arteries.³²

Slight, if any, kidney weight changes were found following the treatment of castrated males with various estrogens.³³ However, estradiol benzoate caused an increase in kidney weight in ovariectomized rats.^{30, 34} Salvini⁷⁶ noted that in the rabbit the kidney damage, which was caused by certain doses of uranium nitrate, was much greater in ovariectomized than in normal animals. After ovariectomy, estrin exerted a protective influence on the kidneys against uranium nitrate.

The estrogens have been shown to have pathologic effects on the kidney. In 1927, degenerative changes were observed in the kidneys of intact rats following the use of follicular fluid and crude ovarian extracts.³⁵ Recently green granules were demonstrated in the tubular epithelium of the kidney after the administrations of diethylstilbestrol to the intact animal.³⁶ The granules were probably the result of the icterus caused by the drug. More recent investigators¹⁰ found that certain doses of estrogens in ovariectomized and intact rats produced peculiar cystlike degenerative changes in the kidneys. These were mostly confined to the boundary layers of the cortex and medulla. Others³⁸⁻⁴⁰ found that natural estrogens and diethylstilbestrol produced a distension of the ureters and resultant hydronephrosis in the intact animal.

The findings on the effect of adrenalectomy on the kidney structure are in variance. Early investigators⁴¹ in 1916, found that adrenalectomy had no effect on the kidney of the cat. However, diuretics given to the cats caused the appearance of degenerative changes. Later, others⁴²⁻⁴⁵ observed degenerative changes in the kidneys of adrenalectomized cats and rabbits. One observer described the changes as a "lipoid nephrosis." More recent work,⁴⁶ however, failed to reveal any characteristic renal lesions in rats following adrenalectomy.

Desoxycorticosterone acetate increased the renal weight of normal male and female rats and prevented the renal weight decrease action of α -estradiol.²⁰ Ludden and his co-workers²² also demonstrated this and noted that the action was greater in males than in females. When given with testosterone propionate, there was an additive effect. The increase was due to hypertrophy and possible hyperplasia of the convoluted tubules. Desoxycorticosterone acetate had a protective effect in experimental uremia after complete nephrectomy.⁴⁷⁻⁴⁹ After complete nephrectomy was done, the survival time was prolonged, the clinical signs of uremia were delayed, and the rise in the nonprotein nitrogen content of the blood was inhibited.

Hormonal influence on the ureter was first considered by Hofbauer⁷⁴ in 1928. He found a marked hypertrophy and hyperplasia of the musculature and connective tissue of the ureteral sheath of the lowest part of the pelvic portion of the ureter in the second trimester of pregnancy. Recently Prather⁵⁰ considered hormonal activity to be responsible for ureteral atony in the first trimester of pregnancy and for other ureteral changes during the remainder of the pregnancy and the post-partum period. Animal experimentation, however, has led to diametrically opposed conclusions regarding the effect of the steroids on the ureter. Payne and Hodes⁵¹ concluded that there was no ureteral dilatation after injections of prolan, estrin and progesterone in the normally pregnant rabbit. Another group⁵² also found that there were no significant changes in the ureters after injections of steroids in castrated dogs as compared to controls. Schmitz⁵³ noted that the influence of hormones on isolated pig ureters was not constant. However, estrogens and progesterone were found by others to inhibit peristalsis and muscular activity of the dog, pig and cow ureters *in vitro*.⁵⁴⁻⁵⁷ In intact mice, natural and synthetic estrogenic substances often produced dilatation and distension of the ureters with resultant hydronephrosis.^{30-38, 58} In the treatment of post-partum pyeloureteral dilatations, the results of stilbestrol administration paralleled an untreated group.⁷⁵ The administration of progestin was productive of very slight regression in only one patient, and in some patients it appeared to increase pyeloureteral dilatation.

Although estrogenic substance effects are primarily manifested in the organs directly concerned with reproduction, structures which have their embryologic origin in the same system may also respond.⁷⁶ The effect of estrogens on the bladder and urethra were described by a number of investigators. Lacassagne⁵⁹ described a progressive proliferation, thickening, and budding of the mucosa in the bladders of a few mice injected with estrone. He thought this to be a direct local effect of accumulated estrone in the stagnating urine. Others found distinct thickening and squamous metaplasia with early keratinization of the epithelium of the bladder in estradiol treated cats and estrone treated mice.^{60, 61} A similar effect on the urethra was found. There was also a marked thickening of the muscular wall with an increase in the size of the muscle fibers. This was considered to be a direct effect of the estrogens. It has been shown that one week after the injection of progynon B, the vesical capacity decreased.⁶² However, the average capacity increased two or three weeks after the injection. This latter finding was noted to occur with some frequency along with dilatation of the ureters and resultant hydronephrosis in mice after the long administration of estrogenic substances.⁵⁸ Hydronephrosis was noted in the intact opossum (*Didelphys virginiana* and *Trichosurus vulpecula*) after estrogenic treatment.^{63, 64} However, the investigators believed that the probable factor was extreme cornification of the urethra causing an obstruction.

The effect of the steroids has been found useful clinically in urinary tract disturbances associated with gynecologic conditions. Estrogen deficient post-menopausal women with urinary symptoms (frequency, dysuria, urgency and incontinence), which were refractory to the orthodox treatment, were treated with estrogens.⁶⁵ The achieved relief of symptoms paralleled the estrogenic effect as evidenced by the vaginal smear. The discontinuance of estrogen therapy resulted in the recurrence of the urinary symptoms and the reappearance of estrogen deficiency as evidenced in the smears. The incontinence was believed to be due to an impairment of the bladder sphincter function on a basis of estrogen deficiency. The other urinary symptoms were due to atrophic lesions of the mucous membrane of the urethral meatus. Following treatment with the estrogens, the mucosa became completely epithelized, like the vaginal mucosa, and the symptoms disappeared.

Steinkamm⁶⁶ recently used estradiol benzoate in an effort to control bladder tone after pelvic operations in women. Little success was noted in attempting to control

the frequent postoperative atony of the bladder after various pelvic operations. The treatment gave benefit, however, in another type of urinary difficulty which often confronts the gynecologist. Estradiol benzoate favorably influenced urinary incontinence which frequently occurred after radical procedures as Wertheim's operation. The effect, he thought, might be due to an improvement in the thickness and tone of the tissue surrounding the urethra.

On the basis of animal experiments, Hoffman and Treite⁷⁸ investigated the influence of estrogens on the bladder tone and capacity of climacteric women. Estradiol benzoate in the form of progynon B was used on nineteen carefully chosen patients. After one injection of five milligrams of estradiol benzoate an average decrease of 35 per cent of the bladder capacity was noted in ten patients. In eight patients there were no noticeable changes, while in one patient there was an increase in bladder capacity. The reduction in bladder capacity was noted on the third day and reached its height between the third and fifth days. In three cases the estrogenic influence persisted for twelve days. An increase of the original dose of five milligrams to ten milligrams did not influence the results. On cystoscopic examination they found an increased vascular injection without any signs of inflammatory reaction. No change in bladder capacity could be determined after corpus luteum therapy. By estrogenic therapy they were also able to improve to a definite extent some cases of relative urinary incontinence in older women.

Moe⁶⁷ and Moucard⁶⁷ were the first to note that functional disorders of micturition of menopausal women could be relieved with testosterone propionate. Recently Greenblatt⁶⁸⁻⁷¹ noted the alleviation of nocturnal frequency in a series of women who were treated with testosterone propionate for various gynecic disorders. Of the twenty-eight women with this syndrome, nineteen had fibromyomata uteri. In the others, there were stigmata of endocrine imbalance as menorrhagia or dysmenorrhea in the premenopausal group and vasomotor disturbances or atrophic vaginitis in the menopausal group. There was no evidence of the presence of cardiovascular-renal disease, anatomic urinary tract defects, genitourinary tract infection, or psychogenic factors. One young surgically castrate female complained of vasomotor disturbances, dysuria, urgency, and marked nocturnal frequency. Amelioration followed therapy with estradiol and progesterone. No consistent results were noted with progesterone therapy. The author believes that patients with nocturia and diurnal distress should receive an ample course of androgens or estrogens if no pathologic basis can be ascertained, or if the syndrome is refractive to orthodox methods of treatment.

The indications seem clear that the possibilities of clinical usefulness of the steroid hormones in influencing the functions of the urinary tract should be adequately explored on the basis of the findings in the experimental animal. Korenchevsky and Ross¹⁰ suggest that androsterone, which has had marked nephrotropic but weak androgenic effects, would be the androgen worthy of the clinical trial. However, another investigator⁴⁸ believes that desoxycorticosterone acetate has the definite advantage over the androgens in certain cases in not exerting a specific effect on the sex organs. It is believed that patients with chronic nephritis in a stationary status would presumably be put in little or no jeopardy by the constant use of testosterone.⁷² Nocturia, frequency, urgency, and incontinence may have a hormonal basis in those that do not have an organic or psychogenic factor present as the cause of these symptoms.⁷⁰ If no organic or psychogenic basis can be found, or if the syndrome is refractive to the ordinary types of therapy, treatment with androgens or estrogens may be tried. The steroids should also be tried in other urinary tract disturbances associated with gynecologic and other disturbances as well as those already reported. They may be of great value in postoperative gynecologic patients with urinary disturbances.

The possible pathologic effects of the steroid hormones on the urinary tract as found in the experimental animal must be kept in mind. Especially must one consider the possibility of dilatation of the ureters with resultant hydronephrosis in humans with the use of estrogens and progesterone in pregnancy. Moreover, a warning was sounded in a recent editorial that the evidence at hand does not justify indiscriminate treatment of albuminuric and other patients with the steroids.⁷²

Summary

Animal experiments have allowed conclusions to be drawn concerning the influence and working mechanism of the steroid hormones on the urinary tract. The series of clinical observations reveal that the steroid hormones are useful in certain urinary disturbances associated with gynecologic disorders. On the basis of the animal experimentations other therapeutic uses may be found for the steroid hormones in urinary tract disturbances associated with gynecologic disorders.

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Selected Abstracts

Sterility

Hotchkiss, Robert S.: *The Male Factor in Fertile and Barren Marriage*, New York State J. M. 41: 564, 1941.

Detailed analyses of the semen of 150 men examined for barren marriage are reported.

The volume of ejaculate averaged 3 c.c. in the fertile group and 2.9 c.c. in the barren group. The average grade of motility was poorer in the barren than the fertile group. The spermatozoa count averaged 64,100,000 per c.c. group as compared to 120,630,000 per c.c. in the fertile group.

The average number of spermatozoa in the ejaculates of barren men was 189,470,000 as compared with 346,020,000 in the fertile men. The average number of oval (normal) spermatozoa in the barren group was 84.17 per cent while the fertile averaged 89.8 per cent. Tapering cells (abnormal) were found in a higher average percentage (10.3 per cent) in the barren than in the fertile group (3.6 per cent).

An assay of fecundity should include a consideration of volume, grade of motility, number of spermatozoa, and percentage of abnormal forms.

J. P. GREENHILL.

Weisman, Abner I.: *Necrospermia*, J. Clin. Endocrinol. 1: 188, 1941.

Weisman states that it has recently been shown that spermatozoa can withstand abnormally low temperatures (0° C., freezing; -196° C., liquid nitrogen; and -269° C., liquid helium) and can survive for as long as 36 to 48 hours at ordinary room temperatures (20 to 23° C.). However, death of spermatozoa after ejaculation may be brought about easily and rapidly by faulty methods of collection. Microscopic examination of the killed sperms leads to the diagnosis of total necrospermia, and the patient may be told he is sterile since all his spermatozoa are found dead (immotile).

J. P. GREENHILL.

Ramos, A. Peralta, and Ramos A. G. Peralta: *Indications and Technic of Artificial Sterilization in Pregnant Women*, Prensa méd. argent. 27: 2347, 1940.

A series of 87 sterilization operations performed during pregnancy is reported. Among 72,553 labor cases five sterilization operations were performed early in pregnancy through the vagina and 16 through the abdomen. In 53 cases, sterilization was carried out at the time of cesarean section. The technique employed in all cases except three, consisted of tubal ligation of the tubes with partial resection. There were two failures in this series.

J. P. GREENHILL.

Wilson, William M.: *Sterility as Affected by Endocrine Disturbances*, West. J. Surg. 50: 6, 1942.

No standardized regime of endocrine therapy for sterility exists. A physician may become encouraged and even enthusiastic over the results obtained in a small

series of cases but is prone to lose faith when further experience indicates that the initial results probably were but a matter of coincidence. The author mentions his own experience with gonadotropic principle of mare serum as a recent disappointment of this character. The possible exception is the use of thyroid extracts in sterile women with low basal metabolic rates.

HUGO EHRENFEST.

Caffier, P.: Sterility Due to Tubal Closure at Uterine End, *Zentralbl. f. Gynäk.* 65: 500, 1941.

The author studied histologic sections removed from the tubes of 16 sterile women in whom physical examination of the adnexa revealed nothing unusual. In 25 of the tubes closed at the uterine end the following conditions obtained:

Adenomyosis of tubes	14
Adenomyosis and chronic salpingitis	3
Chronic salpingitis	4
Endometriosis	3
Adenomyosis of tubes and endometriosis	1

In two-thirds of the cases there was a deepening of the mucosa of the tube with hypertrophic muscular reaction. The rest were divided between inflammation with stricture and endometriosis. The importance of radiography in diagnosis is emphasized, especially for preventing unnecessary operations upon the uterus. None in the series were pregnant three years after reconstructive operations, and it is felt that the operative risk is not consonant with the chances of subsequent pregnancy. In the salpingographic picture the cornu of the shadow is said to be sharper in endometriotic obstruction, while in adenomyosis it is more blunt and stubby.

R. J. WEISSMAN.

Hori, H., Kawamoto, K., and Utiho, I.: Supplementary Study of Sterility, *Jap. J. Obst. & Gynec.* 24: 2, 1941.

The authors made 734 examinations of the semen in 430 patients. They found nonmotile spermatozoa in the vagina as long as 135 hours after coitus. However, in many cases the spermatozoa escaped from the cervix into the vagina, and they were found in the cervix at the same time. The longest period in which nonmotile spermatozoa were found only in the vagina was 38 hours.

The longest period in which motile spermatozoa were found in the vagina was 37 hours, but the longest time in which active spermatozoa were found only in the vagina was 12 hours.

The longest period in which nonmotile sperm were found in the cervix was 27 days and the longest period in which motile sperm were found in the cervix was 30 days.

In 48 of the 237 cases (20.3 per cent) motile sperm were found in the cervix more than three days after sexual intercourse. Hence, if motility is an indication of fertilizing power, it is possible for sperm to fertilize an ovum even three days after coitus.

J. P. GREENHILL.

Rubenstein, Boris B.: The Vaginal Smear—Basal Body Temperature Technique and Its Application to the Study of Functional Sterility in Women, *Endocrinology* 27: 843, 1940.

The cycle of gonadal function is studied in relation to vaginal smear changes and basal body temperature. The method of collecting the vaginal material is

described in detail. Smears are stained by the Papanicolaou technic with minor modifications and are evaluated chiefly through the characteristics of the epithelial cells although varying amounts of bacteria, leucocytes, erythrocytes, and mucus are given subordinate consideration. A description is given with colored illustrations of eight types of vaginal epithelial cells, the variation of which indicate ovulation and estrone and progesterone function. The vaginal smear picture is described in detail for all phases of the menstrual cycle. Limitations and possible errors of the method are discussed.

Basal temperature curves are obtained through daily rectal or vaginal temperature readings taken under exacting conditions. The interpretation of the temperature curves is discussed and normal, anovulatory, and climacteric cycles are illustrated.

According to the method of study, out of 739 cycles studied in a group of 101 women, 338 cycles were anovulatory, with no patient being exempt from at least one, but the author cautions against the application of this ratio to the general population as the group studied were relatively infertile.

Forty-eight cases of sterility studied through 308 cycles resulting in 32 pregnancies, 11 abortions, and no result in 27 are reported. Four of the cases indicated ovulation during menstruation. Four pregnancies and no failures occurred in this group.

With the vaginal smear-basal body temperature technic the author attempts to locate the time of ovulation, to determine hormone deficiency, and then to influence the cycle or ovulation by means of appropriate therapy.

CLAUDE J. EHRENBURG.

Complications of Pregnancy

Gillam, J. F. E.: Ruptured Aneurysm of the Splenic Artery During Pregnancy, *Brit. M. J.* 1: 69, 1942.

The author summarizes 84 cases of ruptured aneurysm of the splenic artery in the literature and adds a case of his own. Of these 85 cases, seven occurred during the last trimester of pregnancy.

The difficulty in diagnosis is emphasized, which is increased by the variability and occasional complete lack of symptoms. Most frequently, colicky pain occurs in the left upper quadrant which is characteristically increased by exertion and by change in posture. Shock, of course, is common. Symptoms referable to the gastrointestinal tract, a pulsating tumor mass and a systolic bruit as occasionally seen.

In 27 cases rupture occurred in two stages: an initial hemorrhage into the lesser sac and a second, and usually fatal, hemorrhage which occurs about two weeks later and ruptures into the peritoneal cavity. The author's case was of this type. Acute left upper quadrant pain followed by signs of profound shock occurred several days before the onset of labor at term. Delivery was uneventful and symptoms subsided. The second hemorrhage occurred on the fifteenth postpartum day. Splenectomy, with removal of the aneurysm was done and the patient recovered.

The author is unable to explain the disproportionately frequent association of pregnancy with this condition.

FRED L. ADAIR AND RAYMOND L. YOUNG.

Martin, J. Purdon: Thrombosis in the Superior Longitudinal Sinus Following Childbirth, *Brit. M. J.* 2: 537, 1941.

The author reviews some of the literature on puerperal thrombosis of the sagittal sinus, and adds three cases of his own.

The diagnosis of sagittal sinus thrombosis has recently become well established. It depends upon signs of increased intracranial pressure and signs of obstruction of the superior cerebral veins. The author feels, however, that many cases are "silent," diagnosis being impossible in our present state of knowledge.

In his search for an explanation of the etiology of sagittal sinus thrombosis in the puerperium, the author has turned to the recent work of Batson. This worker investigated the connections of the pelvic veins by injecting radio-opaque material into the pelvic veins of cadavers. He found that in addition to their known connections with the caval system, the pelvic veins also have free anastomosis with the veins in and around the vertebral canal, so that a pathway was provided for the transmission of the opaque material to the dural sinuses.

Batson further found that when blood flow to or in the inferior vena cava was obstructed by compression, the flow was diverted to the vertebral venous system. He postulated that the same thing would happen during coughing and straining.

Reasoning from these experiments, the author suggests that a fragment of pelvic thrombus in a puerperal patient might easily be carried to the sagittal sinus and there form a nucleus for the formation of a larger clot.

He suggests, therefore, that the parturient woman suspected of having pelvic thrombosis be cautioned against straining, that the abdominal binder be kept loose, and that the patient be kept well propped up in bed.

FRED L. ADAIR AND RAYMOND L. YOUNG.

Prather, G. C., and Sewall, Weston: Recurrent Pyelonephritis, *New England J. Med.* 226: 291, 1942.

In a series of 72 patients a pyelonephritis of pregnancy recurred during subsequent pregnancies in 23 per cent. If the urine becomes sterile during the interval between gestations, the chance of recurrence is less than one in five, if the urine remains infected the chance is about one in two.

There appears no tendency toward hypertension during a subsequent pregnancy as the result of a pyelonephritis of pregnancy.

HUGO EHRENFEST.

Marshak, R. H.: Postpartum Collapse Associated With Abnormalities of the Cardiac Mechanism, With Continuous Electrocardiographic Studies, *Am. Heart J.* 23: 576, 1942.

A 34-year-old white woman with a history of rheumatic fever but no signs of heart disease, is reported to have gone into severe collapse following prophylactic forceps delivery of her second child. Because of extreme tachycardia, a continuous electrocardiogram was taken. This showed a nodal tachycardia with a rate of 215 beats per minute. Eyeball pressure brought about a return of normal rate with extrasystoles. The patient recovered.

L. M. HELLMAN.

Physiology of Pregnancy

Burrows, Harold, MacLeod, Douglass H., and Warren, F. L.: Excretion of Ketosteroids in Human Pregnancy Urine in Relation to the Sex of the Fetus, *Nature (London)* 149: 300, 1942.

The authors state that morning samples of urine, taken from women from eight to twelve weeks pregnant, show different levels of excretion of ketosteroids. These were measured colorimetrically. Twenty women were tested and it was found that

the ketosteroid excretion values could be divided into two groups according to whether the fetuses turned out to be male or female. Fourteen women bearing male fetuses had an average excretion of 26.2 mg. per liter, while 6 bearing female infants had an excretion of 14.2 mg. per liter. The authors state that, while not significantly different, these results are suggestive and that the work should be repeated.

J. M. HELLMAN.

Beruti, Josue A., and Orellana, David: Prediction of Sex According to the Method of Ryoji Itoh, *Arch. Clin. obst. y. ginec. "Eliseo Canton"* 1: 79, 1942.

The results of 44 attempts to prognosticate the sex of a child using the method of Ryoji Itoh are presented. This method, which its originator claims to have given a perfect score (in 15 cases), is based on the presence or absence of proteolytic enzyme in the pregnant woman's urine. This enzyme which hydrolyzes testicular proteins is supposedly present only if the child is a male. Using this procedure, the predictions in the 44 cases were correct 24 times and incorrect 20 times, approximately a chance distribution. The accuracy of the predictions was not influenced by the age of the subjects nor by the interval between the test and the time of delivery. The authors consider the test valueless.

J. P. GREENHILL.

Westberg, V.: Histidinuria—Quick Method for the Determination of Pregnancy, *Acta obst. et gynec. Scandinav.* 112: 180, 1941.

Westberg reviews the Kapeller-Adler method of detecting early pregnancy. A series of 1,023 patients were subjected to the detection of the histidine reaction. The author found that this reaction was negative in 6.3 per cent of healthy pregnant women but if the tests were limited to the first three months of pregnancy, only 3.3 per cent showed negative tests. Urine from nonpregnant women and from men gave negative tests in 98.5 per cent. During the puerperium the histidine secretion rapidly decreased. In a comparison of 171 mice and rabbit pregnancy tests, the histidine reaction compared favorably.

J. P. GREENHILL.

Takenaga, S.: The Process of Fertilization in Humans With Special Reference to the Duration of Pregnancy, *Jap. J. Med. Sc.* Part 1, 94, 1941.

Takenaga reports the occurrence of five pregnancies in the wife of a physician. Carefully examined records of these pregnancies revealed that biologic tests were positive from ten to thirteen days after fertilization. The entrance of posterior lobe hormone into the urine does not occur immediately after fertilization but only after implantation of the egg in the uterus. The duration of pregnancy varied from 262 to 268 days in the five pregnancies. In this particular patient ovulation occurred at irregular times. Thus, pregnancy followed coitus which took place five days after the last day of the last menses, twenty days after this day, twelve days after this day and twenty days after this day, respectively.

J. P. GREENHILL.

Hartman, Carl G.: Non-Effect of Ovariectomy on the 25th Day of Pregnancy in the Rhesus Monkey, *Proc. Soc. Exper. Biol. & Med.* 48: 221, 1941.

On the twenty-fifth day in the monkey the corpus luteum involutes in every normal pregnancy, assuming a smaller volume and more compact internal structure characteristic of the greater part of pregnancy. On the twenty-fifth day of gesta-

tion ovariectomy was done and the corpus luteum was removed (other ovary previously removed). The monkey went to term and a 440 Gm. female baby was born after a normal gestation of 165 days. It was concluded that in the Rhesus monkey the ovaries are not necessary from the twenty-fifth day of pregnancy on for normal gestation, parturition at term, and post-partum involution of the uterus and lactation.

WILLIAM BERMAN.

Nixon, W. C. W.: Diet in Pregnancy, Brit. M. J. 2: 703, 1941.

The author considers pregnancy a "diet efficiency" test. He has studied the effects of diet in pregnancy in various Oriental countries and feels that when the strain of pregnancy is placed upon a woman suffering from a subclinical dietary deficiency, the deficiency frequently appears as a clinical disease.

While this seems true for all vitamin deficiencies, it is particularly true of avitaminosis B₁. In Chinese patients approaching term, the frequency of beriberi is significantly increased over the frequency of this disease in the general population.

The author has long been impressed with the close relationship between toxemia and vitamin B₁ deficiency. Of 42 cases of eclampsia, 19 (45 per cent) were complicated by avitaminosis B₁. Of the 13 fatal cases in this series, 11 were so complicated. On the basis of this and other work, he believes that there is a positive correlation between the severity of a toxemia and B₁ deficiency.

In an effort to improve maternal welfare, the author makes three recommendations: close dietary supervision of prenatal patients, with trained dietitians available for instruction in the preparation of adequate, low-budget diets; practical instruction in modern dietetics for doctors and nurses; and, improvement in hospital diets.

F. L. ADAIR AND RAYMOND L. YOUNG.

Plotz, E. I.: Histidin Excretion in Urine of Pregnant Women, Zentralbl. f. Gynäk. 65: 309, 1941.

Noting the apparently parallel excretion of histidin and prolan in gravid women, Plotz determined qualitative histidin in urine of 100 pregnant and 119 nonpregnant women by the Kapeller-Adler method, (Klin. Wehnschr., p. 1728, 1936). The reaction was positive in 96 per cent of pregnant women and accuracy was improved in the later months of pregnancy. Seven and five tenths per cent were found to have histidinuria. The reaction disappears eight days post partum and six days post abortum. The author feels that negative findings give a more secure basis for ruling out pregnancy than the same findings in the Aschheim-Zondek test. Failures of the test may be expected in hypophyseal tumors, thyrotoxicosis and in the preclimacteric years.

R. J. WEISSMAN.

Zohn, Benjamin: The Relationship of Maternal Diet to Intrauterine Sensitization, J. Allergy 13: 153, 1942.

Certain experimental studies on animals and some clinical observations have supported a belief that during pregnancy some food sensitivities can be started in the fetus by the diet of the mother.

In a study made on 21 pregnant women, Zohn found that excessive consumption of such foods, as chocolate, milk, egg, strawberry, potato, buckwheat, banana, plum, and peach, had no demonstrable effect on the offspring from a viewpoint of sensitization.

Hence any control of the maternal diet during pregnancy aimed at prevention of intrauterine sensitization does not seem justified.

HUGO EHRENFEST.

Vignes, H.: *Ovarian Rhythm During Pregnancy*, Rev. franç. de gynéc. et d'obst. 36: 18, 1941.

The duration of pregnancy is approximately 10 menstrual cycles. There is a mild return of menstruation about a half menstrual cycle after labor and a return of full menstruation about a cycle and a half after delivery. Re-establishment of menstruation after abortion is fairly constant, between one and one and one-half menstrual cycles after the abortion. Spontaneous abortions generally begin during the phase which would have corresponded, if menstruation had continued, with the lutein phase between ovulation and menstruation. Hemorrhages during pregnancy often occur with a periodicity resembling that of menstruation. It is, therefore, not irrational to suppose that ovarian rhythm continues during pregnancy.

J. P. GREENHILL.

Radiation

Kolbow, H.: *Uterus and Vagina in Lateral Roentgenogram*, Zentralbl. f. Gynäk. 65: 748, 1941.

The author has found diagnostic value in lateral films taken with the patient standing, after outlining uterine cavity and tubes with iodized oil, and injecting 10 to 20 c.c. into the vagina. When the patient stands most of the oil flows out, but enough remains to outline the vagina satisfactorily. Exposure 0.6-0.8 sec., kv. 95, P 40, 3.3 mm. Al. filter, 120 Ma. The position of the uterus in relation to vaginal axis is clearly demonstrated, and by filling the bladder to varying capacity, the changes in uterine position may be observed. Active contractions of the vaginal wall were seen after administration of pituitrin, during which the posterior wall became shortened and closely applied to the cervix. The author calls attention to the significance of this mechanism for conception, in contrast to the infantile uterus whose portio does not come in full contact with the receptaculum of the sperm. Retroversion and retroflexion are easily diagnosed, and it is clearly shown that the vagina bends midway to take a more posterior direction in its upper portion.

R. J. WEISSMAN.

Hady-Gediz, M. A.: *Radium in Chronic Cervicitis*, Zentralbl. f. Gynäk. 65: 633, 1941.

The author discusses the complications of the usual treatments of chronic cervicitis. In his Istanbul clinic he has used radium application of 300 mg. hr. with excellent results in a small series of 12 cases. No untoward effects on menses or fertility have been noted. In this series all cases having more extensive inflammation of uterus or adnexae were not included. A second application of 200 to 250 mg. hr. is given six months later for any residual symptoms, although the author does not state how many of his patients required 2 applications. The vagina is cleansed and mucus cleared from the cervix, which is dilated to take Hegar No. 10. A small gauze tampon is passed to the internal os and the radium, in platinum-iridium containers within a 1.5 mm. brass filter tube is inserted in the cervical canal. The deepest part of the tandem contains 5 mg. of radium, followed by two 10 mg. containers. A 1 mm. rubber capsule may be placed over the whole to give some added filtration effect.

R. J. WEISSMAN.

Ehrhardt, K.: *Fetal Organography—Intraamniotic Thorium Injection*, Zentralbl. f. Gynäk. 65: 114, 1941.

The author replaces 8 to 10 c.c. of aspirated amniotic fluid with an equal amount of thorotrast. The colloidal thorium in a four to five months pregnancy becomes

diluted approximately 1:25 and is seen shortly after injection as a diffuse shadow outlining the amniotic sac. In cases of fetal death subsequent films reveal no changes. The living fetus, however, is constantly imbibing amniotic fluid and after an interval of twelve to forty-eight hours the thorium becomes concentrated in the fetal gastrointestinal canal and radiography of the fetus in utero or after delivery reveals all details of the tract. A good concentration of thorium in the lungs brings out their outlines and gives further evidence of intrauterine "respiration." Ehrhardt believes this contrast injection may be useful in cases in which pregnancy is to be terminated shortly as an aid to more exact knowledge of the fetal status, and intrauterine activity.

R. J. WEISSMAN.

Utzuki, A., and Hashidzume, H.: Roentgenologic Delineation of the Fetal Surface in Utero, *Zentralbl. f. Gynäk.* 65: 194, 1941.

In cases of acute hydramnios and where there was evidence of fetal death or monstrosity, the authors have successfully outlined the fetal surface by injecting 15 c.c. of an organic iodized oil into the amniotic fluid via an abdominal puncture after first drawing off from 1 to 2 liters of fluid. The puncture is made 1 cm. below the umbilicus 3 or 4 cm. lateral to the midline. Three cases are presented with excellent radiographs. Details such as hair, digits, scrotum and penis, eyelids, umbilicus can be seen. Maceration of the skin of a dead fetus is readily determined. There appears to be an affinity between the oil and the fetal skin and vernix. No ill effects upon the mother were noted in the cases cited. The first infant was born dead, spontaneously, the day following the injection. Poly and syndactylia, which were noted on the films, were present, as well as incomplete development of the gastrointestinal tract. In the second case the maceration of the fetus was clearly outlined. Spontaneous delivery of a dead infant occurred three days later. In the third case, with a diagnosis of acute hydramnios the procedure clearly outlined an edematous fetus. The infant was born 18 hours later but died on the following day. This infant had a dextrocardia. Unfortunately autopsy permission was refused. The authors feel the method has great diagnostic potentialities and is possibly harmless to the fetus.

R. J. WEISSMAN.

Breitländer and Heinrichs: Pulmonary Embolism after Iodized Oil Hysterosalpingography, *Zentralbl. f. Gynäk.* 65: 124, 1941.

The authors present a case of accidental intravenous deposition of iodized oil, with survival of the patient. A 57-year-old woman complaining of bloody vaginal discharge of several months' duration had a mass the size of a child's head palpable on the right of the uterus. A diagnostic curettage was done and as the curette sank to a depth of 17 cm. in the corner occupied by the tumor, iodized oil was injected under radiographic control to determine whether the uterus had been perforated. Films taken eighteen hours later showed iodine shadows in the periuterine veins, ovarian veins and continuing upward. Shortly afterward a chest film showed a fine distribution of the contrast medium through the pulmonary vessels. As the patient showed no ill effects from this accident she was subjected to panhysterectomy five days later. At no time were there any palpatory, percussion or auscultatory changes in the lungs and the patient made an uneventful recovery from her operation. The authors calculate that from 10 to 20 c.c. of the material found its way into the venous system. An incidental observation of physiologic interest is the fact that the movement of venous blood in the pulmonary system takes place in concert with left ventricular systole.

R. J. WEISSMAN.

Eastland, William E.: The Role of Deep X-ray Therapy in Pruritus Vulvae, *South. M. J.* 34: 324, 1941.

The medical literature contains few references to the use of deep x-ray therapy in the treatment of pruritus vulvae. In certain types designated as idiopathic, essential or neurogenic, an exact cause cannot be discovered, and the ordinary therapeutic measures are ineffective; here deep x-radiation has been used to advantage. It is not advisable to employ deep x-ray treatment for the pruritus that accompanies leucoplakia and kraurosis.

There was definite symptomatic improvement in six of the seven patients whose clinical course formed the basis for this report; the seventh patient was given a lighter dose of x-ray, and the amelioration of symptoms was only temporary. The factors in the author's technique are, 200 kv., 20 ma, 50 cm., S.T.D. with a tin-copper-aluminum filter equivalent to 2 mm., of copper. Two hundred r. units is given once a week for three or four weeks.

ARNOLD GOLDBERGER.

Labor—Management and Complications

Nakamura, T.: The Effect of Lack of Vitamin C Upon Labor, *Jap. J. Obst. & Gynec.* 23: 176, June, 1940.

The author found that lack of vitamin C during pregnancy resulted in abortion and the lack of this vitamin during the puerperium interfered with the mechanism of involution of the uterus. Most of the young, born of mothers with vitamin C deficiency, were either stillborn or very frail.

Sala, Silvestre Luis: Value of Rectal Examination in Obstetrics, *Arch. Clín. obst. y ginec.* "Eliseo Cantón" 1: 118, 1942.

Sala classifies available authoritative opinions on this subject and finds that they range from a decided partiality for rectal examinations to a complete denunciation of this method with some intermediate opinions favoring the use of both rectal and vaginal examination according to the circumstances. A survey of the opinions of the heads of the maternity hospitals in various countries made by Sciclounoff in 1935 indicated that 91.99 per cent used rectal examination, but not exclusively, while only 7.99 per cent used it exclusively. It was also shown by this survey that the method was chiefly used in Germany, Switzerland and the United States, and that many obstetricians regarded it as a dangerous procedure. Some of the conclusions of this survey are re-examined in conjunction with an analysis of the author's own data comprising 2,000 cases observed in the clinic since 1939 when rectal examinations were first practiced.

Sciclounoff's survey indicates that 72 per cent of the men questioned did not consider vaginal examination more conducive to puerperal morbidity and mortality than rectal examination. The author's survey of 16 published studies on this matter shows that the majority consider rectal examination more favorable, although generally only slightly more so than vaginal examination. He criticizes the data employed in most of these studies because they are not rigidly selected and offers an analysis of his own carefully selected data. This leads, however, to the same conclusion, that puerperal morbidity is slightly lower with rectal examination (6.9 per cent) than with vaginal examination (9.1 per cent). He adds that the publicized dangers of the latter are exaggerated.

Concerning the diagnostic reliability of the rectal method, even its most vigorous defenders concede an average error of 10 per cent. In the 2,000 cases analyzed by the author, rectal examination led to 28.8 per cent inadequate or erroneous

diagnoses. In 80 cases, diagnosis by rectal examination was checked by subsequent vaginal examination and found to be corrected in 31.2 per cent and incorrect in 68.7 per cent; these were, of course, cases which presented diagnostic difficulties. The author considers the inherent difficulty of the method one reason for the high percentage of errors. The paradoxical finding in these data that the percentage of error increased as the skill and experience of the examiner increased he believes occurs because the most difficult cases are reserved for the most experienced and competent men.

Diagnosis of cervical dilatation by rectal examination was faulty in 9.9 per cent of the cases, but analysis showed that the height of presentation is an important factor, the percentage of error in judging dilatation is greatest when the presentation is high. The magnitude of error in diagnosis is sometimes very great, confusion existing between the fully dilated cervix with intact membranes and the undilated, but completely effaced cervix.

Diagnosis of the condition of the membranes is most difficult by rectal examination. The author found 18.2 per cent of error in such diagnoses and again found that the height of the presentation directly influenced the incidence of error.

Diagnosis of the presentation is generally considered easy by the rectal method although occasional gross errors have been recorded in the literature. The author found 1.2 per cent of error in his data and again the proportion of error was greater the higher the presentation. Errors almost always concerned confusion of breech presentations with cephalic. Only 0.3 per cent of error was found in diagnosing the height of the presentation.

The author concludes that rectal examination entails less puerperal morbidity than vaginal examination, but is at a disadvantage in diagnosis. However, the inadequacy of rectal examination in this respect diminishes to reasonable limits if only the factors of cervical dilatation and height of presentation are concerned, the two determinations generally sufficient for conduct of normal deliveries. Vaginal examination, however, is essential for diagnosis in abnormal or doubtful cases.

J. P. GREENHILL.

Vara, P.: Observations on Early Rising After Gynecologic Operations and Labor, *Acta. obst. et gynec. Scandinav.* 112: 168, 1941.

In the Woman's Clinic at Helsingfors, 4,447 women were allowed out of bed very soon after delivery and 795 women were allowed out of bed early after gynecologic operations. Vara found that the incidence of thrombosis was definitely less in these women than in women who were permitted to remain in bed longer after delivery or operation. Likewise, there was improvement in function of the bowels and bladder, and the period of convalescence was shortened.

J. P. GREENHILL.

Thoms, Herbert: Inversion of the Uterus, *Yale J. Biol. & Med.* 14: 399, 1942.

The author reviews the factors tending to produce inversion of the uterus. He emphasizes again that the chief contributing factor is the mismanagement of the third stage of labor. However, a certain incidence of uterine inversion will occur even in expert hands, so called, spontaneous inversion. The author discusses acute and chronic inversion, and mentions the generally accepted methods of treatment for the latter, with manual replacement from below and laparotomy with traction from above being the most common forms of treatment in acute inversion. Two cases of chronic inversion of the uterus are described. ,

WILLIAM BERMAN.

Mehta, Chamam Lal: Management of Breech Presentation by External Version and Its Effects on Prematurity and Mortality of Infants, *J. Indian M. A.* 10: 1, 1941.

The author is in agreement with the general literature that the best treatment for breech presentation is external version. External versions were performed from the twenty-sixth week onward. The thirtieth to the thirty-second week is the best time for attempting external version. The authors feel that breech presentation is a cause of prematurity. The incidence of prematurity in this series was 12.63 per cent (using fetal weight of 5 pounds as a sign). The fetal mortality was higher in the premature than in the mature (25 per cent to 8.42 per cent) The author encountered no complications. There has been a considerable fall in the percentage of premature children and fetal mortality as a result of external version.

WILLIAM BERMAN.

Coventry, W. A.: The Management of the Breech, *Journal-Lancet* 62: 1, 1942.

The author is fully in accord with the method of Potter. He points out several cardinal principles in breech delivery, namely (1) the cervix must be completely dilated or dilatable, (2) complete anesthesia, and (3) the perineum must be completely ironed out. After these things have been done the operator can bring down one or both feet, depending upon the ease of operation. The buttocks should be delivered posteriorly. It is advisable to use steady traction with one hand at the baby's ankle. When the umbilicus is reached, a portion of the cord is pulled down and traction continued. The shoulders are delivered anteriorly. The delivery of the head can take time. The head is delivered either by aid of the index finger in the baby's mouth or by Piper forceps if necessary. Traction should never be placed over the baby's shoulders. The author allows fifteen minutes for a simple uncomplicated breech delivery.

WILLIAM BERMAN.

Fleming, John G.: Previous Uterine Infection as a Predisposing Cause for Spontaneous Rupture of the Uterus, *Ohio State Med. J.* 37: 747, 1941.

Two cases of spontaneous rupture of the uterus at term, in patients with a history of previous uterine infection following term delivery and infected induced abortion, respectively, are reported. Similar pathologic changes of the uterine wall, consisting of marked degeneration and atrophy of the muscle cells and extensive replacement of the myometrium by fibrous connective tissue, were found in both cases. Patients with a history of a previous uterine infection, whether following abortion or term parturition, warrant close observation during subsequent pregnancies and deliveries against the increased incidence of serious complications, including spontaneous rupture of the uterus.

J. P. GREENHILL.

Houston, Craig S.: Report of Bagging Cases at Providence Lying-In Hospital, *Rhode Island Med. J.* 23: 207, 1940.

Among 226 cases (1926 to 1938) where a bag was used, 168, or 30 per cent, were in labor more than twelve hours after the bag was inserted. In this connection it is of interest that in six cases a bag was inserted twice, in two cases the bag was expelled without any dilatation, in two cases the bag broke and in four cases it was removed without having accomplished anything after twenty-four hours. This gives a total of 14 cases in which nothing at all was accomplished in way of dilatation by use of bag.

Thus there were 28 cases where there was not sufficient dilatation obtained by bag for delivery and manual dilatation or cesarean section was necessary. This is in addition to the fourteen cases above mentioned where nothing was accomplished by the bag giving a total of 18.6 per cent where the bag did not give very satisfactory results as far as dilatation of the cervix was concerned.

There was a morbidity of 67 or about 30 per cent. This includes ten cases of severe post-partum shock and six cases of severe sepsis. There were eight cases, or 3.5 per cent, of prolapsed cord after the bag was inserted. The fetal mortality was high, 34 cases, or 59.24 per cent.

There was a total maternal mortality of 19 cases, or 8.4 per cent. Ten of these died during the first three years which this study covers.

In analyzing these cases further there were eleven who had eclampsia or severe toxemia out of 96 cases; seven who had a placenta previa or separated placenta out of 92 cases; and one case of pernicious vomiting.

As a result of this study, the author's opinion is that there is a place for the use of the bag in obstetrics, but it must be remembered that there is considerable risk to the mother and an extremely high fetal mortality. It does not seem advisable to attempt bagging unless the cervix is easily dilatable as failures were frequent with a rigid cervix. In the past few years simple rupture of the membranes has replaced use of the bag in cases of marginal placenta previa where the cervix is easily dilatable, while cases of central and partial placenta previa and cases with a rigid cervix are better treated by cesarean section. The author thinks that the use of a bag is seldom indicated to induce labor or to hasten dilatation of the cervix, as the danger of infection is great and failure of the bag to accomplish dilatation is very frequent.

J. P. GREENHILL.

Dr. Fred J. Taussig died at Bar Harbor, Maine, August 21. An extended obituary will appear in an early issue of the JOURNAL.

Item

American Board of Obstetrics and Gynecology, Inc.

A number of changes in Board regulations and requirements became effective at the annual meeting of the Board, May 20, 1943. Several of these changes are designed to broaden the requirements for candidates in Service. Examples are the allowance of a stipulated amount of credit toward special training requirements for men in Service and assigned to general surgical positions, special training allowances on a preceptorship basis for men assigned to obstetric or gynecologic duties in military hospitals and working under the supervision of Diplomates or recognized obstetrician-gynecologists, as well as credit toward the "time in practice" requirement of the Board to be allowed for time in Military Service.

The Board will no longer require a general rotating internship, but will now accept a one-year intern service, although the rotating internship is preferable. Such services must be in institutions approved by the Council on Medical Education and Hospitals of the A. M. A. Lists of such institutions are published regularly in the Educational Number of *The Journal of the A. M. A.*

The privilege of reopening applications by candidates who have been declared ineligible has been extended to two years from date of filing the application, instead of one year.

The Board has ruled temporarily to excuse men in Military Service from the submission of case records at the stipulated examination times, thereby permitting them to proceed without further delay with the Board examinations. This does not obligate the Board, however, to waive the case record requirement for such candidates. Plans have been made to provide similarly for Service men upon their eventual discharge from the Armed Forces, and to permit the greater use of operations done while in residency or in civilian practice before the War.

The next Part I examination of the Board (written paper and submission of case records) will be held on Saturday afternoon, February 12, 1944, at a place convenient to the location of the candidate, whether he be in civilian or military life. Applications must be in the Office of the Secretary by November 15, 1943, ninety days in advance of the examination date. The time and place of the Spring 1944 (Part II) examination will be announced later.

Prospective applicants or candidates in Military Service are urged to obtain from the Office of the Secretary, a copy of the "Record of Professional Assignments for Prospective Applicants for Certification by Specialty Boards" which will be supplied upon request. This record was compiled by the Advisory Board for Medical Specialties and is approved by the offices of the Surgeons-General, having been recommended to the Services in a circular letter, No. 76, from the War Department Army Service Forces, and referred to as the Medical Officers Service Record. These will enable prospective applicants and candidates to keep an accurate record of work done while in Military Service and should be submitted with the candidate's application, so that the Credentials Committee may have this information available in reviewing the application.

Applications and bulletins of detailed information regarding the Board requirements will be sent upon request to the Secretary's Office, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

PAUL TITUS, M.D., Secretary.

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Original Communications

CONTROL OF PUERPERAL INFECTION IN THE UNITED STATES DURING THE LAST CENTURY*

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ONE hundred years ago, Oliver Wendell Holmes read an essay entitled *The Contagiousness of Puerperal Fever* before the Boston Society for Medical Improvement which today is justly regarded as one of the most important medical contributions ever made by an American. The essay was printed at the request of the Society in the *New England Quarterly Journal of Medicine and Surgery* for April, 1843. A few copies were struck off separately for distribution to friends.

Holmes⁵ tells us that his paper was written in a great heat and with passionate indignation after a discussion in the Medical Society suggested by a case "of a physician who made an examination of the body of a patient who had died with puerperal fever, and who himself died in less than a week, apparently in consequence of a wound received at the examination, having attended several women in confinement in the meantime, all of whom, as it was alleged, were attacked with puerperal fever."

The practical point illustrated in the paper was as follows: *The disease known as puerperal fever is so far contagious as to be frequently carried from patient to patient by physicians and nurses.*

Holmes refers to the work of a long list of British practitioners who had insisted on the contagious character of puerperal fever and laid

*Read at a meeting of the Section of Obstetrics and Gynecology of the New York Academy of Medicine, March 23, 1943, in commemoration of the centennial of the publication of Oliver Wendell Holmes's paper "On the Contagiousness of Puerperal Fever."

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

down excellent rules for prevention. Thus, as early as 1773, Charles White of Manchester recognized the similarity of puerperal fever to so-called "surgical fever," stressed the necessity of cleanliness and the importance of isolation of the sick patient. Gordon, of Aberdeen in 1795, stated that the cause of puerperal fever was a specific contagion or infection and that he had evident proof of its infectious nature. Thomas Denman in 1801 announced that the contagiousness of puerperal fever had long been suspected and was now fully proved. In 1835, Robert Collins of Dublin published the results obtained at the Rotunda Hospital by the use of chloride of lime disinfection, cleanliness and the immediate isolation of sick patients. Collins delivered 10,785 women without one death from puerperal fever as then recognized and with a maternal mortality from all causes of 0.53 of 1 per cent.

Dr. Frederick C. Irving⁶ in his delightful book *Safe Deliverance* calls attention to Sir Thomas Watson's lectures on the Principles and Practice of Physic¹⁶ referred to by Oliver Wendell Holmes, which first appeared in the *London Medical Gazette* for 1842. Watson's ideas on puerperal fever appeared in the issue of February 18, 1842 and illustrate the astonishingly complete views as to the etiology and prophylaxis worked out by the British. Watson believed that cases of puerperal fever occurring in succession to the same practitioner are examples of something more than ordinary contagion, operating through the medium of a tainted atmosphere. He believed them to be instances of direct inoculation and likened the interior of the uterus to a large wound, a concept which dates back to Harvey. The practical lesson which these facts inculcated was, according to Watson, that whenever puerperal fever is rife, or when a practitioner has attended any one instance of it, he should use most diligent ablution, even washing his hands with disinfecting fluid such as a weak solution of chlorine; he should avoid going in the same dress to any other of his midwifery patients and take all those precautions which common sense will suggest against his clothes or his body becoming a vehicle of contagion and death between one patient and another. Watson even suggested the invention of a glove which should be impervious to fluid and yet so thin and pliant as not to interfere with the delicate sense of touch. Should these precautions all prove insufficient, he advised that the practitioner is bound to abandon for a season his vocation.

The rules of conduct laid down by Watson and by Holmes the following year were similar to those previously suggested by Robert Lee in 1831 and by James Copland in 1834. To Oliver Wendell Holmes belongs the credit of presenting for the first time in America, with great force and courage, the evidence that puerperal fever is "communicated from one person to another, both directly and indirectly." Neither Watson nor Holmes mentioned isolation of a sick patient. They both limited their views of the subject to the passage of infection from previous cases. Chloride of lime solution was to be used only after a visit to a sick patient.

Unfortunately Holmes' paper appeared in an obscure medical journal which ceased publication after a year's existence and never obtained a large circulation. The *American Journal of the Medical Sciences*, for

July 1843, gave the essay a favorable review, but the two leading American obstetricians of the day, Charles D. Meigs of Jefferson Medical School, and Hugh L. Hodge of the University of Pennsylvania, attacked the views of Holmes vigorously.

Hodge in a lecture *On the Noncontagiousness of Puerperal Fever* wrote as follows:



OLIVER WENDELL HOLMES

"The result of the whole discussion will, I trust, seem, not only to exalt your views on the value and dignity of your profession, but to divert your minds of the over-powering dread that you can ever become, especially to woman, under the extremely interesting circumstances of gestation and parturition, the minister of evil; that you can ever convey, in any possible manner a horrible virus, so destructive in its effects, and so mysterious in its operation as that attributed to puerperal fever."

Dr. Hodge's lecture was unobjectionable in tone and language but the attack of Dr. Meigs exceeded the bounds of good taste. Meigs ridiculed Holmes' deductions as "the jejune and fizzleless dreamings of sophomore writers."

"I prefer," Meigs wrote in regard to cases of puerperal fever, "to attribute them to accident, or Providence of which I can form a conception, rather than to a contagion of which I cannot form any clear idea, at least as to this particular malady."

Holmes, feeling that his first paper could hardly be said to have been fully brought before the profession, returned to the subject in 1855 when he republished his original essay with a new introduction answering Meigs and with a list of additional references and cases, entitled *Puerperal Fever as a Private Pestilence*. This, as Williams points out, "must be regarded as one of the classics of American literature and one of the most forcible presentations of the subject ever made." It is interesting to note that Holmes refers to a paper read by Arneth before the National Academy of Medicine of Paris on the Means of Disinfection proposed by M. Semmelweis. The use of chloride of lime solution and of the nail brush before admission to lying-in wards, was noted.

In after years, when Oliver Wendell Holmes was famous throughout the country as a teacher, essayist and poet he still remained proud of his old paper on puerperal fever. In a letter to Dr. James R. Chadwick written May 8, 1883, a half century after the publication of his essay, he said,

"I do not know what others have done since my efforts; I do know that others had eried out with all their might against the terrible evil before I did, and I gave them full credit for it. But I think I shrieked my warning louder and longer than any of them, and I am pleased to remember that I took my ground on the existing evidence before the little army of microbes was marched up to support my position."

In the *Professor at the Breakfast Table*, Holmes has the Professor say:

"When, by the permission of Providence, I held up to the professional public the damnable facts connected with the conveyance of poison from one young mother's chamber to another's, for doing which humble office I desire to be thankful that I have lived, though nothing else good should ever come of my life, I had to bear the sneers of those whose position I had assailed and, as I believe, have at last demolished, so that nothing but the ghosts of dead women stir among the ruins."

Over a quarter of a century was to pass after the publication of *Puerperal Fever as a Private Pestilence* before the teachings of Holmes and Semmelweis were carried out although as early as 1857, B. Fordyce Barker in his *Remarks on Puerperal Fever* referred to the work of both. Chloride of lime solution and the use of a nail brush before delivery were still neglected by the profession.

Gunning S. Bedford in his *Principles and Practice of Obstetrics*, 1861, was one of the first American writers of authority to accept the views of Holmes on the contagiousness of puerperal fever. He also refers to Arneth's paper on the work of Semmelweis. Bedford stated:

"The inoculation may be traceable to the hand of the accoucheur carrying the poison into the system during his vaginal explorations." Under certain circumstances, he believed that puerperal fever may originate with the patient herself. He concluded that it is the duty of the medical man "when in attendance on women attacked with the puerperal fever, no matter what his views may be as to the contagious-

ness of the disease, to use every precaution against the possibility of translating the affection through his own person. In this precaution nothing will be lost and much may be gained."

In regard to prophylactic treatment, he referred to the remarkable results obtained in the Dublin Lying-In Hospital under the master-ship of Collins. A firm believer in the isolation of the patient, Bedford wrote: "the separation of the sick from the healthy is, in my opinion, a *sine qua non* to the arrest of epidemic puerperal fever as it prevails in hospital practice."

Perhaps the first paper to appear in the United States on antiseptics in obstetrics was read by Thomas Lothrop⁹ before the Buffalo Medical Club in March 1879. He pointed out that the mortality in the old Marion Street Asylum in New York City from 1856 to 1866 was 1.1 per cent. At the New York Nursery and Child's Hospital the mortality from 1865 to 1876 was 4.1 per cent. He cited the good results obtained by Stadfeld at Copenhagen where the use of antiseptics had been introduced in 1870. Lothrop concluded that puerperal fever could be limited by the free use of antiseptics and that the success of Lister's method of antiseptics in surgery called for the employment of measures founded on the same principles in midwifery.

Henry J. Garrigues⁴ is considered by many writers as the father of antiseptics in obstetrics in this country. He introduced the use of bichloride of mercury at the New York Maternity Hospital in 1883. Just previous to this step, out of 345 women confined, 30 died. Following a series of reforms by Garrigues there were 162 confinements with no deaths and "as by magic all trouble disappeared." Garrigues employing bichloride of mercury as an antiseptic obtained strict disinfection of hands, instruments and dressings. He kept ante-partum patients in wards apart from parturient and puerperal patients. Sick patients were isolated. Far ahead of his time, he taught that there ought to be a special delivery room and that the isolation department should be separated entirely from the common ward and should have special nurses who should not be allowed to enter the wards. He recognized the importance of ventilation. Vaginal examinations were limited. During the delivery sterilized cap and gown were worn as in a surgical operation. From 1884 to 1893 the death rate from infection at the New York Maternity Hospital reached the exceedingly low figure of 0.18 per cent. Following the experience of Garrigues, William T. Lusk,¹⁰ an early advocate of Lister's principles as applied to obstetrics, introduced antiseptic methods at the Emergency Hospital connected with Bellevue in New York and subsequently reported that there had been the greatest possible change in his service. Dr. W. L. Richardson¹² shortly thereafter introduced a similar technique at the Boston Lying-In Hospital.

Lusk tells us that when Garrigues first published the details of his treatment, many took a humorous view of it. T. Gaillard Thomas,¹⁴

however, lent his support to the new doctrine in a paper read before the New York Academy of Medicine on December 6, 1883, in which he advocated that the measures should be employed in private as well as in hospital practice. He was answered by the venerable Fordyce Barker who opposed prophylactic measures and stated "I shall die impenitent."

Antisepsis was soon carried to absurd lengths. Carbolic acid solution was used not only for the hands but for douches during labor and post partum. A pad soaked in the solution was kept applied to the vulva and in some instances the patient was delivered under a carbolic spray. Increasing reliance on antisepsis led to careless manipulation and interference but eventually the disastrous effects of this trend were recognized and cleanliness or asepsis was stressed.

According to Miles H. Phillips¹² we owe the introduction of the face mask to Dr. Joseph B. De Lee of Chicago, who began using it in obstetries following a small epidemic which was traced to the nasal discharge of an intern. The first picture of a mask being used in obstetries is to be found in the third edition of De Lee's textbook, the *Principles and Practice of Obstetrics*, 1918.

The first published account of a bacteriologic investigation of the possibilities of droplet infection in obstetric practice was the paper of A. E. Kanter and I. Pilot,⁷ entitled *Hemolytic Streptococci and their Relation to Pregnancy and the Puerperium*. This work was done at the Presbyterian Hospital, Chicago, in 1923. The authors concluded that droplet infection from attendants is possible and the use of gauze masks during delivery and the exclusion of those having sore throat from the delivery room and from attendance on puerperal women is clearly indicated.

One of the most important and thorough investigations of an epidemic of puerperal infection was made by B. P. Watson,¹⁵ the results of which were published in a paper entitled, *An Outbreak of Puerperal Sepsis in New York City*. From January 16 to February 14, 1927, twenty-four patients out of a total of one hundred sixty-three delivered at the Sloane Hospital for Women, developed streptococcal infection and eight of them died. Cases continued to occur after treatment of the operating and delivery rooms with chloride of lime. A complete bacteriologic examination of the hospital failed to demonstrate hemolytic streptococci in the air, on the floors or walls, in the operating room, in dressings, in supplies, or water. The only place where streptococci were found, other than in the infected patients, was in the nose and throat of certain doctors, nurses and members of the domestic staff. The paper in summary stressed the facts that "it is important to exclude streptococcus carriers from maternity hospitals and to insist on complete masking by all in attendance on parturient or puerperal women." This report had a tremendous influence in introducing the more widespread use of the masks and careful bacteriologic examination.

R. C. Lancefield² advanced our knowledge of the bacteriology of the hemolytic streptococcus when in 1933 she described five groups of streptococci which she designated as A, B, C, D and E—identified by means of a precipitin test. It is now recognized that the group A hemolytic streptococcus is the chief offender in serious streptococcal infections in man.

Of historic importance in the control of puerperal infection is the widespread interest in the improvement of obstetrics which began in the early thirties of the present century following the lead of the Departmental Committee on Maternal Mortality and Morbidity of the Ministry of Health of Great Britain. In 1933, the results of the White House Conference on Fetal, Newborn, and Maternal Morbidity and Mortality was published while in the same year the New York Academy of Medicine Committee on Public Relations issued their report on Maternal Mortality in New York City, from 1930 to 1932. The following year the Advisory Obstetric Council was organized in New York which led to the extremely important activities which the County Medical Societies have carried out through their committees on maternal welfare. E. F. Daily³ has shown that in each of the five years of Federal and State cooperation under the Social Security Act from 1935 to 1939 inclusive, there has been a well marked reduction in the maternal mortality rate and predicts that a rate of less than twenty per 10,000 live births now seems possible of attainment. That rate was reached in New York City in 1941. A similar level has been reached in other communities throughout the country but not in all. Recently the Department of Health of New York announced that in the first seven weeks of 1943 the maternal death rate was 1.9 per thousand births. The work of the Special Committee on Maternal Welfare of the New York County Society in cooperation with the Department of Health and the Maternity Center Association has been outstanding.

For years doctors failed to understand the enlightened views of White, Collins, Holmes and Semmelweis. Mortality from infection mounted following the introduction of anesthesia in 1846 with the subsequent increased ease of operative interference. Even when the role of bacteria in infection began to be understood the teachings of those who led the way were neglected. The road forward has been a difficult one. All students of the history of puerperal infection have recognized the complexity of the problem and the fact that at the present time our knowledge is far from complete. After a century we recognize that the words of Oliver Wendell Holmes are still true. He wrote, "Indifference will not do here; our Journalists and Committees have no right to take up their pages with minute anatomy and tediously detailed cases, while it is a question whether or not the 'black death' of childbed is to be scattered broadcast by the agency of the mothers' friend and advisor. Let the men who mould opinions look to it; if there is any voluntary blindness, any interested oversight, any culpable

negligence, even, in such a matter, and the facts shall reach the public ear; the pestilence-carrier of the lying-in-chamber must look to God for pardon, for man will never forgive him."

The world will long honor Oliver Wendell Holmes for pointing out so eloquently the responsibility of the profession, individually and socially, for the control of puerperal infection.

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205 EAST 69TH STREET

VITAMIN A DURING PREGNANCY, LABOR AND THE PUERPERIUM*

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PREGNANCY increases the need for vitamin A. Content with this knowledge, many clinicians dismiss the problem as academic, for can they not meet readily the needs of pregnancy by prescribing a diet rich in vitamin A and by administration of a generous amount of supplementary vitamin A such as fish liver oil? Except for the economic aspects, which incidentally cannot be dismissed lightly, such a program would fulfill the ordinary requirements of pregnancy. Wartime shortages of foodstuffs which are rich in vitamin A and limited supplies of fish liver oils put an end to haphazard and wasteful practices, and so the problem of actual need during pregnancy becomes practical as well as academic. So far there has not been complete agreement about the magnitude of the need during pregnancy, the manner in which it shall be filled and the consequences of failure to meet it. It is the purpose

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of this paper to determine the normal variations of maternal plasma vitamin A throughout pregnancy, delivery, and the puerperium; to determine the influence of diet and of vitamin supplements on the plasma values; to determine the relationship of certain factors and complications of obstetrics; and finally to present practical suggestions for vitamin A intake during pregnancy.

Review of the Problem

The daily requirement of vitamin A during pregnancy is not known although estimates have been made from data obtained by dark adaptation tests and by nutritional surveys. In this report we shall present estimates of daily requirements as determined by a third method, the photolorimetric assay of plasma vitamin A. In 1935, the Technical Commission of the Health Committee of the League of Nations¹ suggested that the minimal daily requirement was 5,000 I.U. (International Units). This figure has been increased by the Food and Nutrition Board of the National Research Council² who advise an allowance of 6,000 I.U. daily during the last half of pregnancy and 8,000 I.U. daily during lactation. Stiebeling and Phipard³ believe that an intake of 7,500 I.U. of vitamin A per day is necessary during pregnancy.

Many factors are known to influence the availability and utilization of vitamin A and its provitamin, carotene. Booher⁴ has pointed out that foods containing vitamin A are not the least expensive, and that the average intake of these substances varies with the amount of money available for food. Food habits, ignorance, gastrointestinal disturbances, excessive use of mineral oil and other such abnormalities individually or collectively may cause a deficient intake of vitamin A even though economies permit an adequate diet. Exceeding all of these factors in importance at the present time is the enforced restriction of diet by food rationing; further elaboration is unnecessary.

Finally, let us remember that carotene is apparently utilized only after it has been converted into vitamin A, yet individuals vary in their ability to convert the provitamin into the vitamin, hence a diet adequate in carotene does not necessarily insure adequacy for vitamin A. The literature reveals no studies of this process during pregnancy, nevertheless most of our dietary charts are computed, possibly without real basis, on an assumed average ability of absorption and conversion.

It is said that few women receive optimal amounts of vitamin A during pregnancy. An extensive study of dietary inadequacies by Williams and Fralin⁵ showed that 96.5 per cent of a *selected* group of pregnant women failed to obtain 6,000 I.U. of vitamin A daily. A survey, of selected groups of prospective mothers by the Peoples League of Health⁶ showed that of all vitamin deficiencies during pregnancy the one most common was that of vitamin A. Dietary history indicated that rather more than half of all mothers were taking less vitamin A than they required.

The frequency of true vitamin A deficiency during pregnancy is not known, certainly clinical evidences of deficiency are uncommon. In the past, most estimates of deficiency have utilized the physical measurement of night blindness. According to some observers⁷ the amount of vitamin A that will just prevent night blindness is slightly less than minimal requirements, yet dark adaptation and intake of vitamin A are not always well correlated. For example, Williams et al⁸ found that 62 per cent of a group of expectant mothers had a history of "deficient" intake but only 37.5 per cent of these "deficient" mothers had poor dark adaptation. Poor dark adaptation was found in half of the pregnant women examined in a large continental charity hospital,⁹ while contrary evidence was obtained in this country by Hirst and Shoemaker¹⁰ who found but 0.62 per cent of poor visual adaptation in a group of 380 pregnant women.

Newer photocolorimetric methods of chemical assay for vitamin A in the blood plasma^{11, 12} have been widely used for the study of vitamin A metabolism in nonpregnant individuals, but these methods have not been applied to pregnancy except in isolated instances. Hirst and Shoemaker doubted the value of chemical analysis in their hands, but they admitted that lack of experience and certain technical difficulties were responsible for their failure. It is not the purpose of this paper to compare critically, the chemical and physical (dark adaptation) methods of determining vitamin A, or to enter into the discussion of their relative merits. The newer literature of this controversy has been recorded by Haig and Patek.¹³ These investigators could not correlate dark adaptation and blood levels of vitamin A within similar groups of patients but both methods reflected the general trend of vitamin A values. Apparently both methods record quantitative variations in two related but not necessarily identical aspects of vitamin A metabolism. How, then, may plasma vitamin A values be interpreted?

At the present time in this laboratory, we believe that high blood levels of vitamin A are indicative of an adequate intake and, as a rule, adequate storage of vitamin A. On occasion faulty storage or poor utilization of the vitamin might result in excessively high plasma values on ordinary intakes. The plasma value obviously represents the amount of the vitamin in circulation, and when this value remains consistently below the critical level we believe the stores, as well as the blood, are depleted. The significance of intermediate plasma values is not clear; although they indicate a diminished amount of vitamin A in the circulation they probably do not always reflect the condition of the stores.

Method

The photocolorimetric method for determination of vitamin A was chosen for several reasons: In the first place, the experience of several thousand previous determinations had made us thoroughly confident

in the technique. Secondly, individual figures could be relied upon, and finally, it was a method applicable to the outpatient, the patient in labor, in the delivery room, and the puerperal patient. The values for vitamin A and total carotene were determined from the blood plasma by the photocolormetric methods described by one of us (MSK), in 1939,¹² and as applied to obstetric studies by us in 1943.¹⁴ It is important to note that the chemical procedure has become so well standardized that colorimetric readings yielded by a given amount of vitamin A can be duplicated readily in different laboratories. It is equally important to note that the interpretation of these findings in terms of units or weights of vitamin A, varies according to the form of calculation and expression chosen by the investigator. Thus, as we pointed out before,¹⁴ it is possible to compare data from different sources only when both the technique of assay and the method of calculation are uniform. It is well to remember that comparisons must be made within the same sex since there is a sex difference in healthy individuals. The average value for plasma vitamin A in healthy nonpregnant women as determined in this laboratory was 96 I.U. per 100 ml. (henceforth designated as I.U. per cent in this paper), and the range was from 65 to 165 I.U. per cent, mostly from 75 to 120 I.U. per cent. Others^{15, 17} using the same technique and calculations have reported average values of 95, 87 and 87 I.U. per cent in groups of healthy women. We consider a value of 90 I.U. per cent as the lower limit of the "optimal" range for women.

Studies from this laboratory and from others using comparable technique indicate that carotene values for healthy nonpregnant women average near 200 micrograms per 100 ml. (gamma per cent).

Plan of Study

In planning a study which includes the entire period of pregnancy, one has the choice of observing many women at different stages of pregnancy, fewer women throughout pregnancy, or a combination of both methods. Repeated observations of a single individual are usually more illuminating than separate observations of several individuals. This is especially true in a study of this sort where variations within a group are apt to be greater than the variation within an individual. Therefore, our fundamental plan was to observe a small number of women several times during the course of pregnancy.

The study started in July, 1940, and continued through December, 1942. Such a long period was necessary for the determination of seasonal variations, as well as individual variations throughout pregnancy and the puerperium. Over 400 determinations of plasma vitamin A and an equal number of determinations of plasma carotene were made on 215 pregnant women. The women came from various social and economic classes, some private patients, some charity patients and others were "part pay" patients. They represented wide levels of intelligence as well. It is important to note that we made no attempt to obtain random sampling of these classes; on the contrary, we included, deliberately, a large number of patients representative of each class.

Two allied obstacles were met early but neither was serious. In the first place, it was difficult to register patients during early pregnancy. Consequently, it was necessary to include some women who were farther advanced in pregnancy at the time of their initial visit. Secondly, it was difficult to find women early in pregnancy who were deficient

in intelligence, finances and consumption of vitamin A. Obviously, the woman who was interested in obtaining proper prenatal care early in pregnancy was likely to be equally interested in maintaining a proper diet.

Thirty-two patients were observed during the first trimester of pregnancy, 65 during the second, and 75 during the third. The latter number was doubled at delivery by the inclusion of another group of patients who were under observation for the fetal-maternal relationship of vitamin A reported previously.¹⁴ Approximately 75 per cent of the patients who began the study, regardless of the duration of pregnancy, were observed through the remainder of pregnancy and delivery.

Plasma vitamin A was determined on fasting blood samples obtained in the morning. If the patient was receiving supplements of vitamin A, she was instructed to withhold them for at least 12 hours before reporting for blood analysis. Occasionally these supplements were inadvertently taken a short time before delivery; in this event the plasma vitamin A values were unreliable.

Ideally in such a study the amount of vitamin A ingested should be measured, but the difficulties of such measurements are great. Moreover, the ingestion of a given quantity of vitamin A does not necessarily insure its complete absorption and utilization. We had to be content with an estimate of vitamin A intake by careful questioning. On the basis of intake each patient was placed in one of four dietary classes: (1) *Adequate diet*, which supplied in excess of 6,000 I.U. of vitamin A each day and conformed to the standards suggested by the pamphlet "Prenatal Care" published by the Department of Labor;¹⁵ (2) *Fair diet*, which failed to meet the standards of the adequate diet, but was not significantly below the average intake of nonpregnant adults, between 3,000 and 6,000 I.U. of vitamin A daily; (3) *Poor diet*, which included all substandard diets below the fair diet; (4) *Optimal diet*, which alone was adequate or nearly so, but in addition to the good diet the patient received 10,000 I.U. or more of vitamin A daily in the form of fish liver oil.

Results

No attempt was made to determine an average plasma vitamin A value for pregnant women, such a figure would be artificial and meaningless. The significance of this statement will become apparent as results are described.

Diet.—There was correlation between the vitamin A intake and the plasma vitamin A level. For reasons to be mentioned later in this paper, such comparisons have greater significance when limited to a definite time during pregnancy. Therefore, only the results obtained at a common time can be compared. Table I presents the results obtained in 157 women at the time of delivery. Statistical analysis* of these data indicates that there is a significant difference between the plasma vitamin A levels of any two of the dietary groups with one exception—difference could not be determined between the "fair" and "adequate" diets groups, a distinction naturally difficult to establish. On the other hand, the difference between the extremes of diet are great. For example, not a single woman with a diet listed as "poor" had a plasma vitamin A value in the range we consider fully normal for nonpregnant women,

*All data have had statistical treatment. Significance has been determined by customary formulas for "k", "t" or "chi square" according to type of data at hand. Space does not permit inclusion of most of these data.

yet over one-third of the women with the best diet were in this range at the time of delivery. If the four dietary groups listed in Table I are simplified and combined to form two larger groups called "inadequate" and "adequate," we find a significant correlation between the intake of vitamin A and its concentration in the plasma.

TABLE I. SHOWING THE RELATIONSHIP BETWEEN DIETARY LEVELS OF INTAKE AND PLASMA VITAMIN A VALUES AT DELIVERY

DIET		DEFICIENCY RANGE BELOW 60 I.U. %		BORDERLINE RANGE 61 TO 75 I.U. %		SUBOPTIMAL RANGE 76 TO 90 I.U. %		OPTIMAL RANGE ABOVE 90 I.U. %		TOTAL
		NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	NUM- BER	PER CENT	
Poor	Inadequate	20	80	3	12	2	8	0	0	25
Fair		17	36	15	32	11	23	4	9	47
Adequate	Adequate	7	24	11	38	7	24	4	14	29
Optimal		5	9	15	26	16	29	20	36	56
Total		49	31	34	22	36	23	28	18	157

The plasma carotene levels varied directly as the intake of carotene, but there were no significant changes in values within a dietary group during the course of pregnancy (Table II). It is noteworthy that the

TABLE II. MEAN PLASMA CAROTENE VALUES IN RELATION TO DIETARY INTAKE AT VARIOUS TIMES DURING PREGNANCY

DIET	1ST TRIMES- TER		2ND TRIMES- TER		3RD TRIMES- TER		DELIVERY		EARLY PUER- PERIUM		1-2 WEEK PUER- PERIUM		TOTAL	
	NUMBER	GAMMA PER CENT	NUMBER	GAMMA PER CENT	NUMBER	GAMMA PER CENT	NUMBER	GAMMA PER CENT	NUMBER	GAMMA PER CENT	NUMBER	GAMMA PER CENT	NUMBER	GAMMA PER CENT
Poor	14	107	4	103	5	86	18	111					41	106
Fair	18	174	27	202	34	180	59	175	15	179			153	181
Adequate	12	248	35	253	39	262	69	249	20	254	31	228	206	254
Excessive							8	407					8	407
Total	41	177	66	216	78	215	146	202	35	222	31	228	408	228

plasma value of pregnant women with an adequate diet (254 gamma per cent) averaged approximately 20 per cent higher than the value obtained in this laboratory for healthy nonpregnant women (203 gamma per cent).

We were unable to show relationship between the plasma carotene and plasma vitamin A values—a finding in common with results of other groups studied.¹² Any carotene value, however high or low, might be paired with any vitamin A value.

Season.—Seasonal variations in plasma vitamin A values could not be demonstrated. In this connection it was necessary to exclude all patients receiving supplements of vitamin A as these could easily mask seasonal variations. It was also necessary to consider the stage of pregnancy. For example, plasma vitamin A averaged 64.9 I.U. per cent for 50 women who were delivered during the "winter months" (December through May) as compared to 68.8 I.U. per cent for 53 women delivered during the "summer months" (June through November). This difference is without statistical significance.

On the other hand, the carotene level of the plasma, which in contrast to plasma vitamin A does not vary with the progress of pregnancy and is known to reflect short-time changes in intake, showed a distinct and significant seasonal variation (Table III). The average of the carotene

TABLE III. SEASONAL VARIATIONS IN MEAN PLASMA CAROTENE

SEASON	NUMBER	MEAN VALUE GAMMA %	STAND- ARD DEVI- ATION	STANDARD ERROR	COEFFICI- ENT OF VARIA- TION	S.E. OF DIFF.	RATIO R OR (K)
Winter	177	180.6	±74	±5.5	4.1	±8.67	5.9
Summer	172	231.1	±87.5	±6.7	3.8		

values during the "summer months" was 22 per cent higher than the "winter months." In this latitude the high plasma levels correspond roughly with the season in which vegetables are abundant.

Pregnancy, Labor and Puerperium.—The change in plasma vitamin A during the course of pregnancy, labor and the puerperium is striking and significant. Table IV summarizes the results and each section of that table warrants individual attention.

Plasma levels of vitamin A decrease during the course of pregnancy. While individual findings may deviate occasionally from the general trend this statement is definitely true of pregnant women as a group. The decrease in values did not appear to be progressive throughout pregnancy nor did it always appear at the same stage of pregnancy; instead the time of appearance depended, at least partially, on the intake of vitamin A. In other words, *diminished values usually appeared early in pregnancy when the diet was poor and late in pregnancy when the diet was good.* During the first trimester of pregnancy (Table IV), 11 of 43 women with a low average (66 I.U. per cent) value had a low dietary intake of the vitamin; hyperemesis gravidarum accounted for the decreased dietary intake. In the other 32 women the plasma vitamin A

TABLE IV. MEAN PLASMA VITAMIN A IN RELATION TO STAGE OF PREGNANCY AND DIET

DIET	1ST TRIMES- TER		2ND TRIMESTER		3RD TRIMESTER		DELIVERY		EARLY PUER- PERIUM		1-2 WEEKS PUER- PERIUM	
	NUMBER	VIT. A % I.U.	NUMBER	VIT. A % I.U.	NUMBER	VIT. A % I.U.	NUMBER	VIT. A % I.U.	NUMBER	VIT. A % I.U.	NUMBER	VIT. A % I.U.
Poor	11	66	6	64	12	60	25	52	5	70		
Fair	32	90	25	83	29	71	49	68	12	91	4	85
Adequate			17	93	18	80	29	75	6	110	10	102
Optimal			17	99	16	104	56	85	16	110	9	125
Total	43	84	65	88	75	78	159	73	39	98	23	108

Adjoining figures separated by a heavy line, whether in rows or columns, are significantly different according to statistical methods.

averaged 90 I.U. per cent. This value represents the blood levels as the patients reported for their first prenatal visit and it is similar to values obtained in healthy nonpregnant females. After the initial blood sample was taken, each patient was given the customary prenatal advice and was urged to follow the dietary recommendations of the pamphlet.

"Prenatal Care."¹⁸ In addition, some patients were instructed to take supplements of 5,000 to 10,000 and 20,000 I.U. of vitamin A respectively, in the form of fish liver oil concentrates.

During the second trimester, these patients were again observed for plasma vitamin A levels, and each was reclassified according to her dietary intake during the past three months. A few new patients were added. At this stage of pregnancy only those patients who had received an "adequate" or an "optimal" diet maintained a mean plasma vitamin value above the level of 90 I.U. per cent. Those women with "fair" diets, who had failed to meet the qualifications necessary for an "adequate" diet, had an average plasma value slightly but significantly below the optimal level. Plasma values of women having "poor" diets remained very low.

Three months later, during the third trimester, women with "poor" diets had plasma values within the deficiency range; i.e., below 60 I.U. per cent. There was a significant decline in the plasma values of women who received "fair" or "adequate" diets and neither group had maintained optimal blood levels. Only the group of mothers who received an "optimal" (supplemented) diet had plasma values which averaged high. By the time of delivery the plasma values of the women receiving an "optimal" diet had dropped too; however, the average value (85 I.U. per cent) did not fall significantly below the level of 90 I.U. per cent. The averages of blood values within the other dietary groups remained essentially unchanged from the levels of the third trimester.

If values for the end of pregnancy, which are based on determinations made at the time of delivery, are valid, it is necessary to eliminate labor as a cause of sudden, temporary change. Twenty-one women were examined just before or at the onset of labor and again at the time of delivery. Their plasma levels averaged 79 and 72 I.U. per cent respectively; although there was a slight decline in average values, a comparison of these means showed no difference statistically.

Striking changes of plasma vitamin A took place during the early puerperium. In 39 of the patients observed at delivery, the plasma vitamin A determination was repeated within 48 hours; usually the test was repeated about 24 hours after delivery. The shortest period was 6 hours and the longest was 48 hours. Little or no vitamin A was ingested during this interval; supplements were withheld, only limited amounts were eaten and all patients had fasted for at least 14 hours before the second blood sample was withdrawn. Yet in *every* instance the plasma vitamin A had increased during this short period of time. Table V illustrates the mean increase observed in plasma vitamin A. It also presents the results of simultaneous determination of carotene which, in a measure, served as a control. The individual increases of vitamin A varied from 5 to 66 I.U. per cent while the average increase

TABLE V. IMMEDIATE PUERPERAL CHANGES IN PLASMA VITAMIN A AND CAROTENE

	VITAMIN A I.U. %		CAROTENE GAMMA %	
	DELIVERY	PUERPERIUM	DELIVERY	PUERPERIUM
Mean	61.7	93.3	240	220
S.D.	±17.5	±20.4	±82.5	±70
S.E.	± 3.2	±3.8	±5.4	±4.1
Difference Between Means		31.6		20.0
S.E. of Difference		±4.0		±6.8
Ratio R or (k)		±7.9		±2.9

for the group was 31.6 I.U. per cent, an increase of roughly 33 per cent. The plasma carotene during the same interval of time showed a slight but insignificant *decrease*. Vitamin C was also determined on most of these women (data unpublished) and it, like carotene, had a tendency to decrease shortly after delivery.

The later puerperium is not characterized by notable changes in plasma vitamin A levels. Table IV shows the results observed during the second week and Table VI lists individual results of 5 women through the sixth week post partum. All of these patients lactated; they were chosen for study because of lactation, and all but one remained in the optimum range throughout the study with little tendency toward decrease.

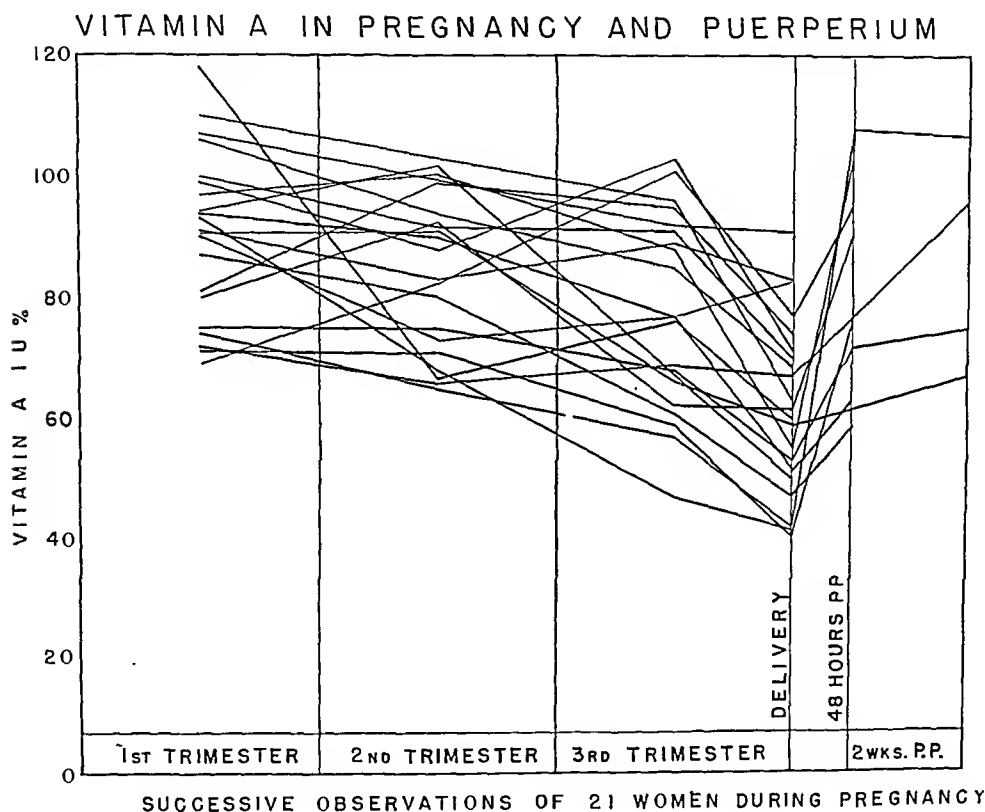


Fig. 1.

The many patients and many assays of vitamin A preclude recording of all individual values; nevertheless, we believe a graphic record of some individuals throughout pregnancy will illustrate more clearly the changes just described. Fig. 1 illustrates the results of 21 representative patients observed throughout pregnancy.

To test the effect of supplements of vitamin A on the plasma values, a group of patients were given 5,000, 10,000 and 20,000 I.U. of the vitamin daily in addition to their usual diet. Table VII shows the individual variations throughout pregnancy. Ingestion of 10,000 I.U. daily kept the plasma values at a more desirable level than did 5,000 I.U.; however, use of 20,000 I.U. had little or no advantage over the use of 10,000 I.U.

TABLE VI. INDIVIDUAL PLASMA VITAMIN A VALUE DURING LACTATION

PATIENT	DIET	10TH PP DAY	20TH PP DAY	30TH PP DAY	40TH PP DAY
1	Fair	110 I.U. %	94 I.U. %	107 I.U. %	123 I.U. %
2	Adequate	93	80	77	70
3	Adequate	118	120	125	125
4	Adequate	144	141	135	121
5	Optimum	131	199	169	156

TABLE VII. SHOWING THE INFLUENCE OF SUPPLEMENTS OF VITAMIN A ON THE INDIVIDUAL PLASMA VALUES (I.U. %)

PA-TIENT	DAILY DOSE I.U.	1ST TRIMES-TER	2ND TRIMES-TER	3RD TRIMES-TER	DE-LIVERY	EARLY PUER-PERIUM	1-2 WEEK PUER-PERIUM
A	5,000	94	102	--	50	--	--
B	5,000	107	--	92	91	116	118
C	5,000	74	65	57	42	108	107
D	5,000	75	75	68	53	72	74
E	5,000	72	66	68	68	65	93
F	10,000	--	114	91	70	--	--
G	10,000	69	84	101	77	95	--
H	10,000	--	84	102	95	--	--
I	10,000	--	99	92	90	127	--
J	10,000	100	91	91	70	--	--
K	20,000	--	155	79	76	118	136
L	20,000	81	102	96	74	--	--
M	20,000	98	87	105	70	--	--
N	20,000	--	104	79	94	--	--
O	20,000	--	122	142	--	139	--

Miscellaneous Studies.—The plasma vitamin A values were studied in relation to some complications of pregnancy. Lack of space prevents a complete presentation of the statistical data but we shall submit a summary of the significant results:

(a) *Hyperemesis Gravidarum.*—Plasma vitamin A averaged 66 I.U. per cent in a group of eleven patients with vomiting of pregnancy. Individual values were 33, 44 and 49 I.U. per cent in patients with severe vomiting while values of 108, 92, 71 and 71 I.U. per cent were recorded in those with milder degrees of emesis. The mean value of 66 I.U. per cent was significantly lower than the mean value of 90 I.U. per cent found for healthy women during the first trimester of pregnancy.

(b) *Toxemia.*—Five late toxemias of pregnancy were observed: one was eclampsia, three pre-eclampsia, and one the hypertensive type. The average plasma vitamin values for the toxemic patients was 72 I.U. per cent. Neither the average nor the individual values were unlike those obtained from healthy women with similar diets during late pregnancy.

(c) *Cesarean Section.*—To rule out the factor of labor as a cause of the early puerperal rise in plasma vitamin A, we observed five women who had never been in labor but were delivered by elective cesarean section. Within 24 hours all five had the customary puerperal increase in vitamin A.

(d) *Anesthesia.*—Most of the women who were studied at delivery and post partum, had received inhalation analgesia and anesthesia. It was necessary to eliminate anesthesia as a factor in the production of the puerperal mobilization of vitamin A. Three patients were delivered without the use of analgesia or anesthesia; all exhibited the character-

istic puerperal rise; which amounted to 31, 41 and 53 I.U. per cent respectively.

(e) *Prenatal Care*.—Of 159 women observed at delivery, 33 had received neither prenatal care nor supplements of vitamin A and their plasma vitamin A averaged 56 I.U. per cent; 78 had received prenatal care but no supplements and their average value was 71 I.U. per cent. The remaining 48 received prenatal care and supplements and showed an average plasma value of 87 I.U. per cent. The differences between these mean values are statistically significant and they confirm an opinion expressed earlier in this paper; i.e. women who were disinterested in obtaining prenatal care and have little knowledge of or interest in a proper diet. Table VIII shows the distribution of values observed.

TABLE VIII. MISCELLANEOUS CONDITIONS OF PREGNANCY IN RELATION TO VITAMIN A VALUES

	VALUES BELOW 90 I.U. %		VALUES ABOVE 90 I.U. %		TOTAL NUMBER
	NUMBER	PER CENT	NUMBER	PER CENT	
(a) Pregnancy with complications	28	100	0	0	28
Pregnancy without complications	98	77	29	23	127
(b) Morbid puerperium	33	91.5	3	8.5	36
Afebrile puerperium	93	77	28	23	121
(c) No prenatal care or supplements	32	97	1	3	32
Prenatal care without supplements	44	88.5	6	11.5	52
Prenatal care with supplements	45	64.4	24	35.5	69

(f) *Complications of Pregnancy and Labor*.—All complications of pregnancy were grouped and compared with the uncomplicated pregnancies. Such grouping is open to criticism, nevertheless the wide variety of complications in so few patients made this necessary. Complications of pregnancy were less frequent when the plasma vitamin A level was high. (Table VIIIa.)

(g) *Morbidity*.—Puerperal morbidity was calculated according to the British Standard. Table VIIIb lists the frequency of morbidity in relation to plasma vitamin A levels. Statistical significance was obtained when the group with values above 90 I.U. per cent were compared with the group below that figure.

(h) *Duration of Labor*.—The duration of labor was in no way associated with the plasma vitamin A values.

Discussion

The preceding results have given evidence of the value of plasma vitamin A determinations as an aid to the clinical study of vitamin A nutrition during pregnancy. In the hands of a competent chemist, the photocolorimetric method of determining the blood values is simple and accurate and our results during pregnancy, as well as those of other workers studying nonpregnant individuals,^{12, 15-17} indicate the utility of the procedure. It is true that the storage and the efficiency with which

the vitamin is used cannot necessarily be estimated by this test; neither can any other single criterion decide these complex problems.

Although we did not attempt to determine the frequency of vitamin A deficiency during pregnancy, we were impressed with the infrequency of such states among our patients. In fact, this study was prolonged because of our desire to include a representative number of patients with a poor vitamin A intake. Two factors which exerted considerable influence in the maintenance of dietary adequacy were economics and education. The first, adequate finances, permitted the purchase of proper foodstuffs and in most cases supplements of the vitamin when necessary. Education—and we do not mean formal education—made the expectant mothers understand the importance of prenatal care. If the patient reported regularly for prenatal care she was usually able to understand the importance of diet and was interested in obtaining the proper foods.

Throughout this study we were able to establish a satisfactory correlation between the intake of vitamin A and the plasma values for groups of patients. This was usually true for individual patients; though occasional unexplained individual deviations were encountered. As a rule, a low intake of vitamin A for a few weeks was followed by low plasma values. For example, not one of twenty-five patients at delivery who had a history of poor vitamin A intake had a blood value which reached 90 I.U. per cent, the beginning of the "optimal" range. Neither was an adequate nor a high intake of vitamin A always accompanied by a high plasma value. On the other hand, if the plasma value was high the patient *usually* gave a history of an adequate intake of vitamin A. Factors other than intake alone help to determine the amounts of the vitamin circulating in the blood at a given time.

As we have said, group values were reliable but individual values during pregnancy were occasionally misleading. Thus, of 56 patients at delivery with a history of optimal intake of vitamin A, 5 had plasma values in the deficiency zone. It is incredible that a vitamin A deficiency could exist when the daily intake of that substance was known to be at least 12,000 to 15,000 I.U.

The need for vitamin A apparently increased as the pregnancy progressed. During the first trimester, a diet which was adequate for non-pregnant women was also adequate for pregnant women, except of course when such complications as hyperemesis gravidarum intervened. During the second trimester, only the best diet met the needs, and during the third trimester there was need for supplements of vitamin A in addition to amounts supplied by the diet. From our studies we concluded that optimal plasma vitamin A levels could be maintained during the last trimester of pregnancy by the addition of 10,000 I.U. of the vitamin each day. Larger supplements, 20,000 I.U. daily were no more ef-

fective. If the supplements provided only 5,000 I.U. of the vitamin daily the plasma values were likely to fall into the subnormal range.

The hydremia which accompanies pregnancy might be considered as a possible cause of the progressive decline in vitamin A blood values; but recall that there was no decline in carotene values of the same patients during the same period of time. The cause of these low individual values at the time of delivery is not immediately apparent, but we shall see in a later paragraph that a storage may be partly responsible for some of these results.

The relationships between carotene and vitamin A of the plasma remain obscure. The ingestion of large amounts of carotene, whether by diet or supplements, elevated the plasma carotene without affecting the plasma vitamin A. Numerous factors are known to influence the efficiency of the human body in converting carotene into vitamin A, but as far as we have been able to determine this problem has not been studied in connection with pregnancy. For that matter it is poorly understood in metabolism of the nonpregnant individual.

The immediate mobilization of vitamin A into the blood stream post partum which we observed was remarkable and provoked much interest and speculation about the mechanism and the significance of the phenomenon. We found but a single common factor to every patient; the emptying of the uterus. At first we thought that the activity of labor might cause this change; but the usual increase in plasma values followed very short and easy labors and also followed delivery by cesarean section of women who had never been in labor. Neither was anesthesia a factor, as women who were delivered without anesthesia or analgesia exhibited the characteristic immediate puerperal increase of plasma values. These results may be compared with those reported by Clausen et al.¹⁹ who stated that anesthesia, trauma and bleeding did not produce significant mobilization of vitamin, particularly as compared with alcohol. The rapidity of the change in plasma concentration of vitamin A, which we observed, eliminates puerperal diuresis as a possible cause. Corroborative evidence was added by the failure of carotene and vitamin C values to change in a parallel direction. We did not attempt to determine the minimal time necessary for mobilization of vitamin A into the blood stream, but it was noted as early as six hours post partum and was usually complete within 24 hours. One understandable exception to this mobilization was noted: In another study, large doses of vitamin A, 60,000 to 330,000 I.U., were given to the mother a short time before delivery in an effort to produce very high plasma levels. This succeeded but these women did not have a higher plasma level in the early puerperium, in fact puerperal values decreased unless the supplements were continued. In such instances perhaps an excess amount of the vitamin was already circulating in the blood stream and more could

not be mobilized from the body stores, or perhaps the artificially induced excess masked any physiologic change.

Puerperal mobilization of vitamin A is probably but one link in the chain of events involving the metabolism of vitamin A during pregnancy, and this mobilization also illustrates another adaptive measure of the body to meet a crucial situation. During pregnancy there must be storage of vitamin A in the tissues, possibly at a rate greater than usual. This storage is one factor which results in decreasing plasma values in the presence of a high intake of the vitamin. In this regard is it possible that the women with normal or high plasma values at the time of delivery have complete loading of tissue stores? The increased need for vitamin A during pregnancy is, of course, another cause of the decline in plasma values. At the time of delivery some mechanism, as yet unknown but associated with the removal of the uterine contents, releases the vitamin from the stores and mobilizes it into the blood stream where it is available for lactation. This idea is further substantiated by the case with which the elevated values were sustained during the puerperium, even in some patients who had low values during pregnancy.

It is both difficult and hazardous to attempt the correlation of pregnancy with the deficiency of a single or even several vitamins. Individual deficiencies are rare; multiple deficiencies the rule. Furthermore, it is difficult to avoid the familiar fallacy of *post hoc ergo propter hoc* in relating vitamin deficiencies to complications of pregnancy. We found no correlation between the toxemias of pregnancy and plasma vitamin A, even though low values might be anticipated because of the liver damage common in some toxemias. Plasma vitamin A levels could not be correlated with the duration of labor. While it is true that the incidence of puerperal morbidity was less if the plasma values were above 90 I.U. per cent at the time of delivery, nevertheless, one should not try to draw definite conclusions from this observation. The importance of prenatal care in the maintenance of proper nutrition must not be overlooked, and low plasma vitamin A values are common in women who have had inadequate attention during pregnancy.

The principles of sound obstetric practice require that all women receive an adequate diet throughout pregnancy, and by adequate we refer to all food substances as well as those rich in vitamin A. Shortages of dairy products and fish liver oils during this war make discriminate use of these substances necessary according to the needs of the individual. From these studies we have devised the following plan for meeting vitamin A requirements during pregnancy and the puerperium: The diet described as adequate by the pamphlet "Prenatal Care" published by the Children's Bureau¹⁵ will supply adequate amounts of vitamin A during the first trimester and probably the second trimester as well. However, for the sake of safety, supplements of 5,000 I.U. of vitamin A daily may be added during the second trimester. During the third

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The immediate mobilization of vitamin A into the blood stream post partum which we observed was remarkable and provoked much interest and speculation about the mechanism and the significance of the phenomenon. We found but a single common factor to every patient; the emptying of the uterus. At first we thought that the activity of labor might cause this change; but the usual increase in plasma values followed very short and easy labors and also followed delivery by cesarean section of women who had never been in labor. Neither was anesthesia a factor, as women who were delivered without anesthesia or analgesia exhibited the characteristic immediate puerperal increase of plasma values. These results may be compared with those reported by Clausen et al.¹⁹ who stated that anesthesia, trauma and bleeding did not produce significant mobilization of vitamin, particularly as compared with alcohol. The rapidity of the change in plasma concentration of vitamin A, which we observed, eliminates puerperal diuresis as a possible cause. Corroborative evidence was added by the failure of carotene and vitamin C values to change in a parallel direction. We did not attempt to determine the minimal time necessary for mobilization of vitamin A into the blood stream, but it was noted as early as six hours post partum and was usually complete within 24 hours. One understandable exception to this mobilization was noted: In another study, large doses of vitamin A, 60,000 to 330,000 I.U., were given to the mother a short time before delivery in an effort to produce very high plasma levels. This succeeded but these women did not have a higher plasma level in the early puerperium, in fact puerperal values decreased unless the supplements were continued. In such instances perhaps an excess amount of the vitamin was already circulating in the blood stream and more could

not be mobilized from the body stores, or perhaps the artificially induced excess masked any physiologic change.

Puerperal mobilization of vitamin A is probably but one link in the chain of events involving the metabolism of vitamin A during pregnancy, and this mobilization also illustrates another adaptive measure of the body to meet a crucial situation. During pregnancy there must be storage of vitamin A in the tissues, possibly at a rate greater than usual. This storage is one factor which results in decreasing plasma values in the presence of a high intake of the vitamin. In this regard is it possible that the women with normal or high plasma values at the time of delivery have complete loading of tissue stores? The increased need for vitamin A during pregnancy is, of course, another cause of the decline in plasma values. At the time of delivery some mechanism, as yet unknown but associated with the removal of the uterine contents, releases the vitamin from the stores and mobilizes it into the blood stream where it is available for lactation. This idea is further substantiated by the ease with which the elevated values were sustained during the puerperium, even in some patients who had low values during pregnancy.

It is both difficult and hazardous to attempt the correlation of pregnancy with the deficiency of a single or even several vitamins. Individual deficiencies are rare; multiple deficiencies the rule. Furthermore, it is difficult to avoid the familiar fallacy of *post hoc ergo propter hoc* in relating vitamin deficiencies to complications of pregnancy. We found no correlation between the toxemias of pregnancy and plasma vitamin A, even though low values might be anticipated because of the liver damage common in some toxemias. Plasma vitamin A levels could not be correlated with the duration of labor. While it is true that the incidence of puerperal morbidity was less if the plasma values were above 90 I.U. per cent at the time of delivery, nevertheless, one should not try to draw definite conclusions from this observation. The importance of prenatal care in the maintenance of proper nutrition must not be overlooked, and low plasma vitamin A values are common in women who have had inadequate attention during pregnancy.

The principles of sound obstetric practice require that all women receive an adequate diet throughout pregnancy, and by adequate we refer to all food substances as well as those rich in vitamin A. Shortages of dairy products and fish liver oils during this war make discriminate use of these substances necessary according to the needs of the individual. From these studies we have devised the following plan for meeting vitamin A requirements during pregnancy and the puerperium: The diet described as adequate by the pamphlet "Prenatal Care" published by the Children's Bureau¹⁸ will supply adequate amounts of vitamin A during the first trimester and probably the second trimester as well. However, for the sake of safety, supplements of 5,000 I.U. of vitamin A daily may be added during the second trimester. During the third

trimester the supplements should be increased to 10,000 I.U. daily, but there is no evidence that amounts greater than this are necessary under usual conditions.

If the provitamin can be efficiently converted into the vitamin, it should be possible to maintain satisfactory vitamin A nutrition during pregnancy by the ingestion of sufficient carotene alone. However, since evidence is accumulating which suggests that conversion as well as absorption are not uniformly efficient, we favor a diet which supplies generous amounts of vitamin A itself rather than one which depends principally on conversion from carotene. Under ordinary living conditions, a diet rich in vitamin A can be obtained by the proper selection and consumption of dairy products, liver, eggs, etc. During war-time conditions, it is necessary and important that the pregnant women receive these foodstuffs. If the proper diet cannot be maintained then the need for vitamin A, at least, can be met by increased supplements of fish liver oil.

Most estimates of the need for vitamin A during the puerperium, particularly during lactation, are very high, higher than at any other time during pregnancy. Results of this study and of other unpublished data indicate that this idea may be wrong. It is true that small to moderate amounts of vitamin A may be "lost" through secretion of milk, but only those clinicians who practice obstetrics and pediatrics realize fully how few women are able to supply the newborn infant with enough milk for more than a few days or weeks. Our studies of pregnancy and lactation indicate that the woman does not require as much vitamin A during the puerperium as during pregnancy, and unless there is unusually abundant production of milk an "adequate" diet post partum will supply the needs. If lactation is plentiful the addition of 5,000 units of vitamin A to the diet may be of value. It is well to remember that the general nutritional and caloric requirements are greater during lactation, and the woman should receive plenty of the necessary foodstuffs for the maintenance of good general nutritional standards during the puerperium.

Summary and Conclusions

1. Plasma vitamin A values during pregnancy reflect in general the dietary intake of the vitamin.
2. As the pregnancy progresses the vitamin A values decrease, but the appearance of the decrease is delayed according to the adequacy of the diet. Storage of the vitamin plus increased demands of pregnancy probably account for the observed decrease in blood values.
3. Mobilization of the vitamin into the blood stream occurs within 24 hours post partum. Following the immediate puerperal mobilization of vitamin A, the values are usually well maintained during the remainder of the puerperium.

4. There was no correlation between plasma vitamin A and carotene values. The relationship between these two substances in the blood stream remains obscure.

5. Complications of pregnancy and labor, and puerperal morbidity were less frequent when the plasma levels remained above 90 I.U. per cent; however, it is hazardous to attribute the responsibility of cause to a vitamin deficiency when many other factors are involved also.

6. Plasma vitamin A values were generally low in women who had not received prenatal care.

The ingestion of an adequate diet according to accepted standards provides enough vitamin A to maintain normal blood values during the first trimester. During the second trimester 5,000 I.U. of vitamin A daily are necessary in addition to an adequate diet. This amount should be increased to 10,000 I.U. during the last trimester. Needs during the puerperium can usually be supplied by a good diet alone unless lactation is unusually abundant and prolonged.

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COMPARATIVE BLOOD SUGAR STUDIES IN THE PARTURIENT WOMAN AND THE NEWBORN INFANT

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DURING the past quarter century, several articles have appeared in medical literature dealing with blood sugar in the parturient woman and the newborn infant.

In 1917, Morriss,¹ using the Lewis and Benedict method, established that normal blood sugar values prevailing in pregnancy and the puerperium were 90 to 110 mg. per cent and that the mean maternal blood sugar at the moment of birth was 132 mg. per cent, approximately one-third greater than that obtained during pregnancy and the puerperium. It was further concluded by him that there was a definite rise in blood sugar in direct proportion to the duration of labor; in labors of less than seven hours the blood sugar was 123 mg. per cent and in longer labors the mean value was 136 mg. per cent, the determining factor appeared to be the length of the second stage.

He also found that in women delivered under chloroform anesthesia the blood sugar was 137 mg. per cent. In newborn blood obtained from the placenta and from the severed cord, with duplicate analyses from the umbilical vein (arterial blood), the mean value was 115 mg. per cent. With the mother under anesthesia, the average was 125 mg. per cent and without anesthesia it was 110 mg. per cent.

Rawley,² in 1923, using a modified Benedict method, confirmed the work of Morriss regarding maternal blood sugar but found that in thirty-two cord specimens the average blood sugar was 90 mg. per cent. He felt that anesthesia was a contributing but not a determining factor in the rise of blood sugar and that asphyxia produces a more marked rise than anesthesia with ether.

Revesz and Turolt,³ in 1926, using the Burg modiproters method, found the blood sugar in twelve women at the end of the second stage of labor to be 140 mg. per cent; in the umbilical vein it was 115 mg. per cent and in the umbilical artery 94 mg. per cent. They concluded that the blood sugar is increased during labor and that if the blood sugar in the mother is high it will usually be high in the fetus. The fetus, however, develops its own capacity for sugar and is independent of the mother.

Holman and Mathieu,⁴ in 1933, using the Osgood modification of the Schaeffer micromethod, found the average blood sugar in one hundred women at the end of the second stage of labor to be 102 mg. per cent and the sugar in the cord blood to be 90 mg. per cent.

Ketterham and Anstin,⁵ in 1938, using the Jeghers-Myers modification of the Folin-Mahrius micromethod, found in 50 women an average blood sugar of 124 mg. per cent at the end of the second stage

of labor and in the cord of 47 newborn an average of 103 mg. per cent. They concluded that labor and anesthesia alone or combined caused a rise in blood sugar at delivery and that the blood sugar is higher at delivery than during the first stage by a mean difference of 28 mg. per 100 c.c.

From the foregoing it appears that we may conclude that these investigators have shown that long labors produce a greater rise in maternal blood sugar than labors of relatively short duration; that blood sugar in the mother is affected by the use of drugs for analgesia and anesthesia. With the exception of the work of Revesz and Turolt, who studied both arterial and venous blood in the cord, it appears to us that the true picture of the blood in the newborn has not been given; that generally speaking when we use cord blood we get arterial blood only from the umbilical vein because the umbilical arteries so contract that it is impossible to get venous blood.

Methods and Materials Used in This Study

The patients used in this series were taken from the obstetrical service of the Los Angeles County Hospital. They were not consecutive cases but were chosen so that the professional staff could secure all blood specimens before 11:00 P.M. An attempt was made to secure reasonably normal cases. The maternal blood was obtained from the median basilic vein at the moment of delivery. Fetal blood was obtained by doubly clamping 12 inches of cord, cutting and handing it to an assistant, who secured specimens of both arterial and venous blood in separate syringes, as shown in Fig. 1.

Subsequent specimens from the newborn were obtained by fontanel puncture for the macromethod and from the heel or finger for the micromethod. Practically all specimens were obtained by the same trained technician so as to eliminate, as far as possible, errors in technique. As soon as secured, all blood specimens were placed in labeled test tubes which had previously been treated with a preservative* and were subsequently sent to the laboratory for the blood sugar determination.

The patients were divided into three groups. In the first group the macromethod was used, the technique being that of Folin and Wu. The Klett-Summerson photoelectric colorimeter was employed, using the blue filter No. 42. The calibration curve was based on the Bureau of Standards analyzed glucose. Maternal and cord blood were taken simultaneously, at the time of delivery, and fontanel blood from the infant six hours after delivery, the baby receiving no nourishment in the interim.

In the second group the micromethod was used, the technique being

*PRESERVATIVE.—Ewing, Mary E. (Laboratory of the Metropolitan Life Insurance Co.) A Method of Collecting and Preserving Small Blood Samples for Glucose Determinations. *J. Lab. & Clin. Med.* 18: 521, 1933. Sodium fluoride and mercuric chloride in proportions of 1 to 0.1% respectively as suggested by Lax, H., and Szirmai, I.: *München. med. Wchnschr.* 76: 58, 1929, were used. 1½ c.c. of an aqueous solution of 4 per cent NaF and 0.4 per cent HgCl₂ freshly prepared was placed in each collection tube (5 in. culture tubes) where the sample to be used ranged from 3 to 5 c.c. Four tenths c.c. of the same solution was placed in 4 in. culture tubes for the preservative for samples containing less than 1 c.c. of blood. These tubes were dried in a 110° oven, stoppered and kept until used. The blood samples were kept in a refrigerator except during the period of transportation from the hospital and at the time the sample was being run.

All blood sugar determinations were made in the Department of Biochemistry at the University of Southern California under the direction of Professor Deuel.

the Jeghers-Myers modification of Folin-Malurius,[†] maternal and cord blood being taken simultaneously, at the time of delivery, and six hours later a specimen from the heel or finger of the infant, the baby receiving no nourishment in the interim.

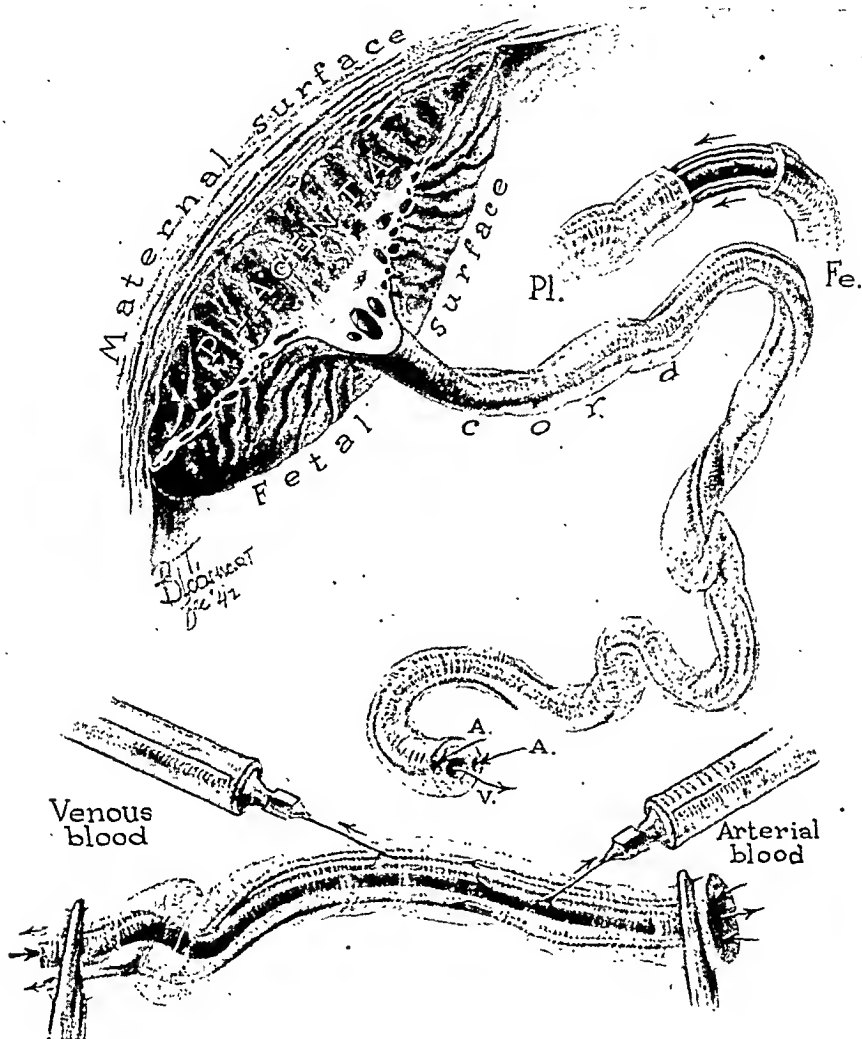


FIG. 1.

In the third group the micromethod was used again, maternal and cord blood being taken simultaneously at the time of delivery and a specimen from the heel of the infant one hour later and again six hours after delivery, no nourishment having been given the baby in the interim.

[†]MICROMETHOD.—Jeghers, H. J. and Myers, V. C.: A Reduction in the Amount of Blood Required for the Folin Micro Blood-Sugar Method. *J. Lab. & Clin. Med.* 15: 982, 1929-30. This method was modified slightly in our laboratory by doubling the final dilution (Adelle Davis). A Folin-Wu blood sugar tube was used and the dilution made to the mark (25 c.c.) in place of a dilution to 12.5 c.c. as suggested in this paper. The color range at this dilution was found more satisfactory for use in a Klett-Summerson photoelectric colorimeter. This dilution was taken into consideration in calculating the Mg. per cent of glucose. The green filter No. 54 was used as suggested for the determination of Prussian blue in the Klett-Summerson booklet. Bureau of Standards glucose was used in determining the calibration curve for this method and a new curve was determined for each new gum ghatti solution employed.

TABLE I. PRIMIPARA—MACROMETHOD

CASE NUMBER	PRENATAL COND. MOTHER	ANALGESIA AND ANESTHESIA	HOURS OF LABOR	TYPE OF DELIVERY	COND. OF BABY AT BIRTH	BIRTH WEIGHT IN GRAMS	BLOOD SUGAR MG./100 C.C.				WEIGHT ON DISC'G	
							M.	UMB. VEIN	U. ART.	FONT. BLOOD & UR.	GRAMS	GRAMS
695-814	Good	Scop. Nemb.	27	Spont. & Epis.	Good	2610	141	119	94	76	2550	
696-083	Good	Scop. Nemb.	9	L.F. & Epis.	Good	3238	121	121	113	58	3253	
697-369	Good	Scop.	9	L.F. & Epis.	Poor	3368	101	126	138	81	3458	
606-258	Good	Scop. Nemb.	20½	Spont. & Epis.	Good	3034	98	98	78	66	3064	
704-778	Good	Nemb.	9	L.F. & Epis.	Good	2914	114	113	93	62	3024	
705-065	Good	None	16	Spont. & Epis.	Good	3722	88	72	62	60	3563	
699-680	Good	Scop. Nemb.	22	Breech, P. & Epis.	Good	3318	110	109	114	55	3288	
698-273	Tox.	Scop. Nemb.	11	L.F. & Epis.	Good	2984	132	103	92	58	2909	
664-446	Good	Scop. Nemb.	20	Spont. & Epis.	Good	3518	114	97	93	81	3383	
684-023	Lucs	Scop. Nemb.	23	L.F. & Epis.	Good	3178	138	114	114	59	3036	
699-755	Good	M. S. & S. & N.	25	L.F. & Epis.	Good	4022	108	90	101	78	3912	
593-688	Good	None	5	Spont.	Good	3238	91	100	86	53	3193	
707-632	Good	Scop. Nemb.	5	L.F. & Epis.	Good	3194	124	128	122	66	3074	
711-981	Good	None	7½	L.F. & Epis.	Good	4086	125	113	100	70	3074	
Average			15			3316	115	108	99	66		3203

TABLE II. MULTIPARA—MACROMETHOD

CASE NUMBER	PRENATAL COND. MOTHER	ANALGESIA AND ANESTHESIA	HOURS OF LABOR	TYPE OF DELIVERY	COND. OF BABY AT BIRTH	BIRTH WEIGHT IN GRAMS	BLOOD SUGAR MG./100 C.C.				WEIGHT ON DISC'G GRAMS	
							M.	UMB. VEIN	U. ART.	FONT. BLOOD G HR.		
337-458	Good	Scop. Nemb.	E 46	Spont. & Epis.	Good	3064	92	84	72	55	2754	
463-725	Good	Scop. Nemb.	E 9	Spont.	Good	3348	88	80	63	80	3238	
711-092	Good	Nemb.	E 4	Spont. & Epis.	Good	3288	91	81	61	61	3064	
21-523	Good	None	E 10	Spont.	Good	3722	98	77	70	60	3690	
245-001	Good	None	E 13	Spont.	Good	3722	102	86	76	63	3927	
703-872	Good	None	E 5½	Spont.	Good	2924	92	96	76	52	2916	
423-150	Good	None	E 3	Spont.	Good	4680	94	90	67	95	4086	
439-780	Good	Scop. Nemb.	E 10	Spont.	Fair	3772	96	91	91	81	3717	
699-209	Good	Scop. Nemb.	E 9	Difficult Shoulder	Fair	3108	104	111	104	72	3158	
699-057	Good	Nemb.	E 4	Spont.	Good	3078	124	118	124	78	2935	
647-149	Good	Scop. Nemb.	E 13	Spont.	Good	3218	93	116	116	54	3378	
699-180	Good	Nemb.	E 6	Spont.	Good	2984	100	78	85	66	3238	
74-430	Good	None	E 8	Spont.	Good	3034	109	84	79	62	2915	
700-472	Good	Scop. Nemb.	E 0 6½	Spont.	Good	3722	85	80	68	54	3757	
684-735	Good	Scop. Nemb.	E 7	Spont.	Good	2640	97	83	70	67	2580	
704-992	Good	None	E 2	Spont.	Good	3144	99	109	92	64	3238	
704-275	Good	None	E 9	Spont.	Good	3114	116	82	64	62	3019	
701-118	Good	Scop. Nemb.	E 10	Breech Ext.	Good	2754	126	110	104	70	2754	
712-094	Good	Scop.	E 4	Spont.	Good	2814	88	82	70	66	2784	
Average			9			3270	99	91	82	66	3218	

TABLE III. PRIMIPARA—MICROMETHOD

CASE NUMBER	PRENATAL COND. MOTHER	ANALGESIA AND ANESTHESIA	HOURS OF LABOR	TYPE OF DELIVERY	COND. OF BIRTH	BIRTH WEIGHT IN GRAMS	BLOOD SUGAR MG./100 C.C.				WEIGHT ON	
							M.	UMB. VEIN	U. ART.	FINGER 6 HR.	HEEL	DISC'G GRAMS
715-337	Good	Scop. Nemb.	9	Spont. & Epis.	Good	3114	175	135	116	62		3348
715-264	Good	Scop. Nemb.	9	Breech & Epis.	Good	2784	131	123	116	72		3004
684-918	Fair	Scop. Nemb.	43	Spont. & Epis.	Good	3912	133	90	61	42		3872
716-182	Good	Scop. Nemb.	33	L.F. & Epis.	Fair	3064	151	159	139	58		3060
706-961	Good	Nem.	48	L.F. & Epis.	Good	3263	128	108	102	82		3408
696-214	Good	Seconal	34	L.F. & Epis.	Good	2610	116	101	100	88		2620
716-894	Good	Scop. Nemb.	8	Spont.	Poor	3208	124	108	92	78		3413
652-947	Good	Scop. Nemb.	28	Scanzoni, Forcep	Good	3263	178	181	178	98		3368
716-995	Good	Scop. Nemb.	23	L.F. & Epis.	Good	3548	151	130	125	72		3942
533-582	Good	Scop. Nemb.	7½	L.F. & Epis.	Good	2894	120	120	106	74		2794
691-782	Good	Scop. Nemb.	21	L.F. & Epis.	Poor	2550	154	138	128	110		2784
692-191	Good	Scop. Nemb.	12	Spont. & Epis.	Good	3488	108	86	59	53		3288
94-178	Good	Scop. Nemb.	8	L.F. & Epis.	Poor	3568	124	117	113	71		3483
719-989	Tox.	Scop. Nemb.	43	L.F. & Epis.	Poor	3747	171	144	117	82		3847
640-190	Good	Scop. Sec.	13	Spont.	Good	3568	167	140	115	52		3293
721-554	Good	Scop. Nemb.	11	Spont. & Epis.	Good	3094	160	142	136	84		3203
721-714	Good	Scop. Nemb.	8	Spont. & Epis.	Fair	3408	129	98	83	56		3223
726-263	Good	Scop. Nemb.	32	L.F. & Epis.	Good	3263	195	165	161	102		3395
Average			21			3241	145	127	114	74		3300

TABLE IV. MULTIPARA—MICROMETHOD

CASE NUMBER	PRENATAL COND. MOTHER	ANALGESIA AND ANESTHESIA	HOURS OF LABOR	TYPE OF DELIVERY	COND. OF BABY AT BIRTH	BIRTH WEIGHT IN GRAMS	BLOOD SUGAR MG./100 C.C.				WEIGHT	
							M.	UMB. VEIN	U. ART.	HEEL FINGER 6 HR.	ON DISC'G GRAMS	
713-907	Good	Scop. Nemb.	E 40	Spont.	Good	3378	98	85	82	69	3428	
505-291	Good	Scop. Nemb.	E 22	Spont.	Good	3458	133	97	80	61	3428	
597-514	Good	Scop. Nemb.	E 7	Spont.	Good	3238	113	88	74	56	3408	
286-958	Good	None	E 3	Spont.	Good	3632	119	83	50	51	3692	
715-158	Good	Scop. Nemb.	E 11	Spont. & Epis.	Good	3178	99	88	71	53	3178	
608-050	Good	None	E 73	Breech Ext.	Good	3114	100	74	88	35	3034	
715-084	Good	None	E 9	Spont.	Good	2186	110	88	78	46	2440	
433-885	Good	Scop. Dial	E 5	Spont. & Epis.	Good	3208	86	83	80	60	3238	
562-964	Good	Scop. Dial	E 7	Spont.	Good	3150	98	70	52	76	3124	
382-427	Lues	None	E 3	Spont.	Good	3518	106	81	73	57	3478	
716-379	Good	Scop. Nemb.	E 9	Spont.	Good	3972	84	63	48	51	3720	
47-425	Good	Scop. Nemb.	E 28	Spont.	Good	3832	83	82	66	58	3792	
717-028	Good	Nemb.	E 6	Spont.	Good	3717	90	74	53	70	3548	
716-583	Good	Scop. Nemb.	E 15	Spont.	Good	2984	122	108	95	79	3144	
559-146	Good	None	E 9	Spont.	Good	3662	100	110	90	80	3518	
647-205	Good	Nemb.	E 18	Spont.	Good	3747	116	117	84	119	3717	
451-546	Good	None	E 10	Spont.	Good	2640	124	112	88	65	2665	
616-671	Good	Nemb.	E 7	Spont. & Epis.	Good	2924	126	112	114	70	3834	
717-823	Good	Scop. Nemb.	E 13	Spont.	Good	3488	105	96	68	88	3488	
721-008	Good	Scop. Nemb.	E 4	Spont. & Epis.	Good	2979	165	152	121	95	3134	
668-562	Good	Nemb.	E 18	Spont.	Good	3687	133	144	89	116	3458	
720-854	Good	Nemb.	E 7	Spont. & Epis.	Good	1926	176	128	125	83	2550	
721-122	Good	Scop. Nemb.	E 14	Spont.	Good	3458	144	129	118	88	3772	
212-331	Lues	Scop. Nemb.	0 4	Spont.	Good	3717	117	92	80	67	3518	
695-934	Good	Scop. Nemb.	E 5	Spont.	Good	2665	151	128	109	71	2724	
351-596	Good	Scop. Nemb.	E 23	Spont.	Good	3488	151	133	94	71	3508	
719-666	Good	Scop. Nemb.	E 24	Spont.	Good	3573	144	113	121	97	3408	
721-713	Good	Scop.	E 6	Spont.	Good	3004	137	122	118	81	3024	
722-327	Good	Scop. Nemb.	E 8	Spont.	Good	3632	105	96	82	85	3348	
608-383	Good	Scop.	E 12	Spont.	Good	3144	121	108	97	80	3378	
436-424	Good	Scop.	E 2	Spont.	Good	3912	130	114	84	55	3912	
171-707	Good	Scop. Nemb.	E 3	Spont.	Good	2754	97	92	68	67	2839	
488-698	Good	None	E 2	Spont.	Good	3488	161	129	115	92	3857	
Average			13			3286	120	103	85	73	3312	

TABLE V. PRIMIPARA—MICROMETHOD

CASE NUMBER	PRENATAL COND. MOTHER	ANALGESIA AND ANESTHESIA	HOURS OF LABOR	TYPE OF DELIVERY	COND. OF BABY AT BIRTH	BIRTH WEIGHT IN GRAMS	BLOOD SUGAR MG./100 C.C.				WEIGHT ON DISC'G	
							M.	UMB. VEIN	D. ART.	1 HR.	HEEL FINGER 6 HR.	GRAMS
727-356	Good	Scop. Nemb.	10	L.F. & Epis.	Good	3119	159	139	130	62	86	2904
728-298	Good	Nemb.	23	L.F. & Epis.	Good	3488	123	122	106	76	84	3852
729-468	Lues	Scop. Nemb.	12	Breech Extract	Good	3717	116	104	84	44	60	3662
728-997	Good	None	39	Spont. & Epis.	Good	2834	148	134	142	138	80	2964
703-044	Tox.	Scop. Nemb.	7	L.F. & Epis.	Good	2864	124	110	99	52	90	2994
732-549	Good	Scop. Nemb.	5	Spont.	Good	3632	121	102	90	89	62	3348
531-891	Good	Scop. Nemb.	15	L.F. & Epis.	Good	3263	141	118	99	58	65	3433
733-659	Good	Scop. Nemb.	11	L.F. & Epis.	Good	4146	136	123	112	109	80	4027
733-354	Good	Scop. Nemb.	32	Spont. & Epis.	Good	4286	149	131	114	104	70	4032
732-315	Good	Scop. Nemb.	31	Spont.	Good	3428	274	170	154	84	81	3558
Average			16			3482	135	120	108	81	75	3408

TABLE VI. MULTIPARA—MICROMETHOD

CASE NUMBER	PRENATAL COND. MOTHER	ANALGESIA AND ANESTHESIA	HOURS OF LABOR	TYPE OF DELIVERY	COND. OF BABY AT BIRTH	BIRTH WEIGHT IN GRAMS	BLOOD SUGAR MG./100 C.C.				WEIGHT ON	
							M.	UMB. VEIN	U. ART.	1 HR.	FINGER	HEEL 6 HR.
623-022	Fair		25	Version Ext.	Good	3263	142	131	105	112	71	3238
Twin					Good	2695	142	143	135	112	61	2695
728-319	Good	Scop. Nemb.	12	Spont.	Good	4196	120	102	89	86	91	4256
721-477	Good	Scop. Nemb.	12	Spont.	Good	3802	125	123	110	113	72	3593
727-335	Good		18	Breech Ext.	Good	3149	116	98	83	58	70	2979
670-780	Good	Scop. Nemb.	6	Spont.	Good	3912	114	100	82	82	88	3662
728-466	Good	Scop. Nemb.	16	Spont.	Good	4820	109	135	122	106	97	4820
728-684	Good	Scop. Nemb.	12	Spont.	Good	4625	114	115	81	59	58	4625
728-754	Good		25	Spont.	Good	3149	114	90	93	82	83	3185
719-543	Good	Scop. Nemb.	16	Spont.	Good	3433	127	102	92	80	75	3548
636-173	Good		14	Spont.	Good	3692	104	108	94	66	89	3662
730-048	Good		8	Spont.	Good	2690	125	106	98	76	94	2724
673-240	Good		5	Spont.	Good	4426	108	114	98	64	84	4186
643-220	Good	Scop. Nemb.	19	Spont.	Good	3178	136	85	100	52	85	3064
540-313	Good		22	Spont.	Good	3408	117	106	81	69	88	3602
614-314	Good	Scop. Nemb.	10	Spont. & Epis.	Good	3578	124	109	80	66	74	3458
729-199	Good	Scop. Nemb.	8	Spont.	Good	3717	100	72	70	54	76	3742
729-352	Good		8	Spont.	Good	4086	111	89	70	73	93	3652
730-183	Good		15	Forcep.	Poor	4116	140	113	97	58	96	Died
222-219	Tbc.		24	Spont.	Good	2500	112	90	77	66	70	2580
401-692	Good		5	Spont.	Good	3972	130	113	82	61	76	3862
730-865	Good		5	Spont.	Good	2550	102	94	98	90	71	3114
576-485	Good	Scop. Nemb.	25	Spont.	Good	3004	103	90	75	61	107	3004
31-255	Good		12	Spont.	Good	3742	136	108	81	62	79	3882
729-530	Good	Scop. Nemb.	27	Spont.	Good	3802	113	85	66	60	73	3802
514-678	Good	Scop. Nemb.	5	Spont.	Good	3692	124	92	85	85	92	3747
669-542	Good	Scop. Nemb.	8	Spont. & Epis.	Good	3378	151	133	122	120	110	3288
719-626	Good	Scop. Nemb.	13	Spont.	Good	4196	184	148	127	68	75	4027
279-662	Good		6	Spont.	Good	3518	112	101	85	91	52	3692
733-192	Good	Nemb.	4	Spont.	Good	3119	142	122	106	70	98	3004
733-976	Good		5	Spont.	Good	3747	121	105	88	82	81	3717
246-817	Good	Scop. Nemb.	55	Spont.	Good	3912	117	101	81	71	67	4256
278-764	Good	Scop. Nemb.	7	Spont.	Good	2724	126	120	96	126	82	2650
734-320	Good	Scop. Nemb.	55	L.F. & Epis.	Good	2206	202	181	163	141	76	2580
699-605	Good	Scop.	5	Spont.	Good	2660	114	93	69	45	66	2660
Twin				Breech Ext.	Good	3598	114	106	82	111	89	3722
Average			15			3510	125	109	93	80	81	3493

TABLE VII. SUMMARY TABLE SHOWING AVERAGE BLOOD SUGAR VALUES

SERIES NO.	NO. OF CASES	BLOOD SUGARS IN MG. PER CENT*				
		SAMPLE 1	SAMPLE 2	SAMPLE 3	SAMPLE 4	SAMPLE 5
I. (Macro-Folin-Wu)	33	106.3 ± 2.6	97.8 ± 2.8	88.3 ± 3.0	66.1 ± 1.7	
II. (Modified Micro-Folin-Wu)	51	128.7 ± 3.8	111.3 ± 3.7	95.8 ± 4.2	73.1 ± 2.6	
III. (Modified Micro-Folin-Wu)	45	126.8 ± 3.0	111.7 ± 2.9	96.4 ± 3.1	77.5 ± 1.8	80.3 ± 3.7

*Including standard errors of mean calculated by the following formula:

$$\text{S.E.M.} = \sqrt{\frac{\sum D^2}{N}} \bigg/ \sqrt{N}$$

D = Deviation of each observation from average.
N = Number of determination.

Sample 1—From mother at time of birth.

Sample 2—From umbilical vein.

Sample 3—From umbilical artery.

Sample 4—Peripheral blood 6 hours after birth.

Sample 5—Peripheral blood 1 hour after birth.

Results

In assembling these data, one must remember that we are dealing with obstetrics as practiced today in a teaching institution. The general policy on the obstetrical service is to give a moderate amount of analgesia during the first stage of labor. In these series nembutal gr. 3 to 6 was used, along with seopolamine hydrobromide gr. $\frac{1}{150}$ to $\frac{1}{100}$. At the termination of the second stage of labor all patients receive anesthesia. In these groups ether was used. Generally speaking, all primiparous women are delivered following an episiotomy, and multiparous women if it is thought necessary. In a fair per cent of these cases forceps were used, and other operative procedures whenever indicated.

In the first group of patients, in which the maeromethod was used, there were 14 primiparas and 19 multiparas. The results, along with other pertinent data, are shown in Tables I and II. In the second group, in which the micromethod was used, there were 18 primiparas and 33 multiparas, as shown in Tables III and IV. In the third group, in which the micromethod was also used, there were 10 primiparas and 34 multiparas, as shown in Tables V and VI. These three series, or groups, are then summarized and the average blood sugars are shown in Table VII, along with the standard error of mean.† Finally an attempt was made to see if there was any direct relation between birth weight and the average blood sugar of the newborn. These results are shown in Table IX. Table VIII shows a statistical average of the blood sugars.

†Case No. 732-315 in Table V is not considered in the average. According to Dunn,⁶ when the deviation of the sample in question from the mean of the remaining samples exceeds 3.29 (6 + 3 PE_s), one is justified solely from statistical considerations in excluding such a value as an atypical one. In this case $6 = 20.4$, PE_s = 3.24 and the greatest deviation which logically can be expected, i.e., 3.29 (6 + 3 PE_s), is 99.1. Therefore any value exceeding the average, 126.8 mg., by more than 99.1 mg. or a total value of 225.9 can be ruled out. Value in question is 274 mg. A variation from the mean of 126.8 which would exceed 99.1 mg. would not occur more than once in 2000 observations. These values are calculated as follows:

$$6 \text{ (Standard deviation)} = \sqrt{\frac{\sum d^2}{n}}$$

d = deviation from mean
n = number of observations

$$\text{PE}_s \text{ (Probable Error of Standard Deviation)} = +0.6745 \frac{6}{\sqrt{2(n-1)}}$$

TABLE VIII. STATISTICAL COMPARISON OF AVERAGE BLOOD SUGAR VALUES

SERIES NO.	M.D.; S.E.M.D. WHEN FOLLOWING AVERAGE BLOOD SUGAR VALUES OF VARIOUS SAMPLES ARE COMPARED*									
	1-2	1-3	1-4	1-5	2-3	2-4	2-5	3-4	3-5	4-5
I	2.23	4.19	12.92		2.16	9.72		5.85		
II	3.28	5.80	12.05		2.77	8.44		4.58		
III	3.62	7.04	14.12	9.77	3.61	10.05	6.68	5.28	3.33	0.68

*M.D.: S.E.M.D. refers to ratio of mean difference to standard error of mean difference; when this ratio exceeds 3.00, the differences are considered highly significant. These values are calculated as follows:

$$S.E.M.D. = \sqrt{(S.E.M._1)^2 + (S.E.M._2)^2}$$

$$S.E.M. = \sqrt{\frac{\sum D^2}{N}} / \sqrt{N}$$

D = Deviation of each observation from average.

N = Number of observations.

M.D. = Difference in values of various averages of blood sugar samples.

TABLE IX. AVERAGE BLOOD SUGAR MG./100 C.C. OF NEWBORN, COMPARED WITH BIRTH WEIGHT

BIRTH WEIGHT IN GRAMS	NUMBER OF CASES	AT BIRTH		PERIPHERAL BLOOD 6 HR. AFTER BIRTH
		UMB. VEIN	UMB. ART.	
Less-2500	3	132	122	68
2500-3000	26	110	98	74
3000-3500	50	111	99	74
3500-4000	38	100	83	72
Over-4000	12	112	98	82

Discussion

In reviewing these series of patients, it appears to us that as a rule the use of anesthesia and analgesia definitely increases the maternal blood sugar. We feel also that long labors and hard operative deliveries likewise tend to increase it; however there are exceptions. The basis for our statements here is the increased blood sugar in the primipara as compared with the multipara, the latter having less analgesia and anesthesia and the length of labor being much shorter.

Regarding the newborn, blood from the umbilical vein was consistently higher in blood sugar than that from the umbilical artery, averaging about ten per cent. This, one would anticipate because the blood coming from the placenta is exposed to a higher blood sugar level in the mother than that returning to the placenta from the fetus. It was particularly interesting to note the drop in blood sugar in the infant after birth. In series three the blood sugar had dropped from an average of 111.7 mg. per cent in the umbilical vein and 96.4 mg. per cent in the umbilical artery at birth to 80.3 mg. per cent in peripheral blood at one hour after birth. At the six hour period after birth in this series it had dropped to 77.5 mg. per cent. In both other series the drop for the six hour period was slightly greater. It was interesting to note that in 22 of these 130 babies the blood sugar at six hours after birth had dropped below 60 mg. per cent and that in three of them it was 35, 42 and 46 mg. per cent respectively. However, none of these showed evidence of shock, and all were discharged from the hospital at

the end of ten days in good condition. Twitchings of the extremities in the newborn have often been attributed to low blood sugar. This was not borne out by our observations.

Because of the fact that before the advent of insulin mothers with diabetes gave birth to abnormally large babies, high blood sugar has been associated with large babies. We were not able to substantiate that in this group of patients.

It will be seen in Table IX that, irrespective of weight, all blood sugar values in the newborn in this series lie within the range of normal.

Summary

A series of patients are presented on which blood sugar determinations were done simultaneously, at the time of delivery, on the mother and the baby; also one hour and six hours later, respectively, on the infants. Two methods of blood sugar determinations were used.

1. Using the maeromethod, there was an average maternal blood sugar of 106.3 mg. per cent and by the mieromethod 128.7 mg. and 126.8 mg. per cent respectively.

2. Blood taken from the umbilical vein at the time of birth averaged 97.8 mg. per cent by the maeromethod and 111.3 mg. and 111.7 mg. per cent, respectively, by the mieromethod. Blood taken from the umbilical artery showed an average of 88.3 mg. per cent by the maeromethod and 95.8 mg. and 96.4 mg. per cent by the mieromethod.

3. Blood obtained one hour after delivery, from the heel or finger of the infant, showed an average of 80.3 mg. per cent by the mieromethod.

4. Blood obtained from the fontanel six hours after delivery showed an average of 66.1 mg. per cent, by the maeromethod, and from the heel or finger of the infant 77.1 mg. and 77.5 mg. per cent, respectively, by the mieromethod.

5. While all of our averages were slightly higher by the use of the mieromethod, we feel that it is an easier and perhaps a more accurate method. We feel also that the use of the photoelectric colorimeter helps to eliminate a portion of human error.

6. In spite of a large number of very low blood sugars we did not note any untoward symptoms in these infants.

7. Our studies do not show that an increase in the weight of the newborn causes an increase in the blood sugar.

The authors wish to express their gratitude to the Resident Staff in Obstetrics and Pediatrics of the Los Angeles General Hospital for their assistance in obtaining these blood samples.

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BOWEN'S DISEASE OF THE VULVA

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IT IS the purpose of this paper to record six cases of Bowen's disease of the vulva occurring in the material of the gynecologic department of The Sloane Hospital for Women. Little is known about this lesion, as it occurs rather infrequently. In reviewing the literature, scattered case reports are found in the German, French, Scandinavian, Italian and South American journals. Comparatively little interest in this disease has been manifest in this country outside of dermatologic circles. The presence of six cases on file in our pathologic department indicates that this lesion should be of some interest to gynecologists.

From January, 1938, through January, 1943, twelve cases of primary epitheliomata of the vulva have been observed. During this interval, the six cases of Bowen's disease were noted.

In 1912, Dr. John T. Bowen¹ called attention to a peculiarly striking and specific skin lesion not previously described. The two cases reported at this time were both males, and the lesions were present on the buttocks and forearm. The clinical course of the patients, the detailed gross and histopathologic findings were beautifully described by Bowen and little new in the way of description has been added since then. Clinically, the disease runs a protracted course, the lesions having been present for as long as 29 years with remissions and exacerbations. Local irritation and discomfort are present. The striking feature of many cases, especially those involving the vulva, is pruritus. Grossly, the lesions may be confused with a variety of dermatologic lesions such as syphilis, tuberculosis, eczema, Paget's disease and psoriasis. Careful observation of details will, in most instances, exclude these lesions. The following characteristics should arouse suspicion of Bowen's disease: i.e., discrete or confluent, flat or slightly elevated, crusted papulo-squamous patches with circinate or serpiginous margins. Surrounding induration of the skin is minimal. On removing the crusts, which peel away easily, a dull red, smooth, moist surface is found, scattered throughout which are pinpoint pearly elevations. The lesions may present a patchy distribution. Healing in the center, with cicatrization, may occur. The lesions tend to spread along the surface peripherally. About the vulva, the lesions in the early stages may suggest leucoplakia or kraurosis. On mucosal surfaces, the lesion frequently manifests itself as a superficial granular, red, eroded, spreading lesion. Removal of the granulations reveals a moist, shiny surface.

The histopathology, as described by Bowen, is quite striking. A marked hyperkeratosis is found. In the deeper areas of this horny plate are seen foci of parakeratosis. The stratum lucidum and granular layer are variable and may or may not be well defined. The character-

istic feature of the *stratum Malpighii* is its marked hypertrophy. This zone is much thicker than normal. The rete Malpighii are club shaped, and dip rather deeply into the subjacent stroma. Striking alterations in the cells making up this zone are noted. All normal tendencies toward stratification are lost. The cells are piled one on top of another in a haphazard fashion. The basal cells are usually normal, but commencing just above them the epithelial cells, up to the surface, have lost their orientation completely. Alterations in the individual cells are quite striking. Marked inter- and intracellular edema is present. Often one sees small groups of 4 to 6 rather large bean-shaped nuclei clumped together in a disorderly fashion. Frequently, mitotic figures of bizarre types occur. Many of the nuclei are disc-shaped, hyperchromatic structures surrounded by clear spaces, the "corps rondes" of Darier. At times, only dustlike grains representing nuclear fragmentation are seen. Changes also occur in the corium. The papillae present numerous small, congested vascular channels. The subpapillary zone often reveals a dense round-cell infiltration, made up chiefly of plasma cells and lymphocytes. Characteristically, the basement membrane is intact.

Following Bowen's report, Darier³ reported three cases involving the skin. The subject has been well reviewed by Yoshida¹³ in 1929, Stout³¹ in 1939, and Cipollaro³³ in 1940. It was not until 1922, that the first case involving the vulva was reported. This was described by Hudelo, Oury and Cailliau.² Since then, sporadic cases have been recorded in the foreign literature.

The following table gives, in chronological order, cases of Bowen's disease of the vulva recorded in the literature to date (Table I).

A total of twenty-six cases is noted. The ages varied from 25 to 73 years, the average being 48.3 years. The duration of symptoms covered the wide span of three months to eleven years, with an average of 4.6 years. The commonest symptom is seen to be pruritus. A consideration of the type of therapy will be taken up later.

The cases reported by Gutmann,⁶ Fuhs,⁷ Goldberg,²⁴ and Marques,²⁵ were all associated with epitheliomata. Delbanco's case is considered questionable. Stout³¹ has observed a case of Bowen's disease of the floor of the mouth in which, in spite of an intact basement membrane on serial sectioning of the entire lesion, metastases occurred subsequently in the cervical lymph nodes, reproducing the histopathology of the original lesion.

Case Reports

Case 1.—Unit No. 676335. A 37-year-old white gravida 0, first seen December 10, 1941, because of pruritus vulvae and vaginal discharge. Patient had been treated for years for trichomonas infection with a variety of ointments, including merthiolate and 3 per cent ammoniated mercury, boric acid, etc. The vulva became inflamed following use of ammoniated mercury. Gentian violet was then tried, alternating with calamine. Pruritus continued.

On March 13, 1942, a small ulcer was noted on the fourchette and perineum. No palpable inguinal nodes were noted. Biopsy on May 5, 1942, revealed Bowen's disease.

On May 8, 1942, a vulvectomy was performed.

Patient was last seen September 16, 1942. She was asymptomatic. There was no recurrence.

TABLE I. SYNOPSIS OF CASES FROM THE LITERATURE

AUTHOR	AGE	LOCUS	DURATION	SYMPTOM	APPEARANCE	THERAPY	RECURRENCE
Hudelo (2) Oury Cailliau 1922	55	Labium Majus	11 yrs.	Pruritus	Typical	Curettage Biopsy	Rapid
Richon (4) 1925	66	Right Labia		Pruritus	Typical with Kraurosis		
Richon (4) 1925	43	Fourchette		Pruritus	Kraurosis Ulceration		
Gutmann (6) 1925	73	Vulva Left Labia			Papillary Crusted	Excision	Associated with epithelioma
Delbanco (7) 1925	59	Vulva					
Dartiguez (8) Mircouches 1926	42	Labium Minus Fourchette			Typical 2.5 cm.	Excision	None
Bloch (9) 1926	71	Vulva	1 yr.		Typical with leucoplakia	Radiation	
Szathmary (10-12) (Rusch) 1928	36	Labium Minus	11 yrs.	Pruritis Pain	Typical	Three Local Excisions, Antiluetic	Yes
Guhrauer (14) 1929	45	Labium Minus	1 yr.		Typical		
Arzt (15) 1929	40	Left Labium			Typical		
Nicolas (16) Massia Rousset 1930	34	Labia Majora	5 yrs.	Pruritus	Typical	Radiated, twice 4,500 r. No filter 28 cm.	Recurred in 10 wks. Then none in 2 yrs.
Nicolas (16) Massia Rousset 1930	50	Vulva	Long	Pruritus	Typical	4,500 r. No filter 16 cm.	
Geiger (17) 1930	62	Left Labia	9 mos.	Pruritus	Typical		
Fuhs (17) 1930	35	Labium Minus			Papillary	Excision	None
Müller (19) 1932	35	Left Labia	3 mos.	Pain Pruritus	Papillary	Partial Vulvec- tomy	
Rothman (20) 1933	56	Vulva	11 yrs.	Pain Pruritus	Typical	Radiated Excised 3 times	Yes
Pozzo (21) 1934	70	Left Labia					
Arzt (22) 1936	57	Left Labium	4 yrs.	Pruritus	Papillary		
Ramel (23) 1936	47	Clitoris	1 yr.		Typical	1,300 r. 160 k.v. 3 m.a. 5 mm. Al.	
Goldberg (24) 1937	38	Vulva	2 yrs.	Pain	Epithelioma Papillary	Radium, Antiluetic	Yes
Daubresse (25) Morelle & Dupont 1937	60	Labia	10 yrs.	Pain	Typical	2,500 r. over 10-day period	None
Levy- (27) Franckel & Martinan 1938	25	Vulva & Anus	2 yrs.	Pruritus	Typical	Excision	
Ferreira (28) Marques 1938	60	Left Labia Anus	4 yrs.		Typical	Excision	
Carrera (30) 1939	72	Vulva Right Labia	3 yrs.	Pruritus	Typical		
Lampe (32) 1940	66	Labia Majora		Pruritus		Excision	
Lutz (34) 1941	66	Right Labium Minus & Anus	2 yrs.	Pruritus Pain	Typical Leucoplakia	Excision	

Pathology No. 17874. Microscopic sections of vulvar lesion revealed typical changes, characteristic of Bowen's disease as described above. (Fig. 1.)

Case 2.—Unit No. 614960. A 45-year-old white woman was first seen in June, 1940, because of pruritus vulvae of two weeks' duration. The patient's husband, a physician, noted a small plaque of leucoplakia near the fourchette. On examination, a well-circumscribed area of leucoplakia was found in the skin of the fourchette. This was surrounded by a well-defined zone of hyperkeratosis. Within the leucoplakic area, which measures 2 by 1 cm., there was a zone of denser leucoplakic changes. No inguinal nodes were palpable.



Fig. 1.—(Case No. 1.) Low power view of lesion showing hyperkeratosis, parakeratosis, thickened rete Malpighii with mitoses, corps ronds, loss of stratification and intact basement membrane ($\times 250$). Insert shows detail of cells under high power ($\times 700$).

On June 15, 1940, wide excision of local area was carried out. The patient has been seen regularly since operation. She is asymptomatic and no recurrence has been noted.

Pathology No. 15106. Microscopic sections of tissue revealed typical Bowenoid changes.

Case 3.—Unit No. 609831. A 35-year-old white woman first seen in May, 1940, because of an ulcerating pruritic lesion of right labium majus of several months' duration. Examination revealed a discrete circinate elevated bright red scaling lesion about 3 cm. in diameter. No inguinal nodes were palpable.

Biopsy revealed a typical Bowen's disease. A vulvectomy was performed on May 16, 1940. There is no evidence of recurrence to date.



Fig. 2.—(Case No. 3.) Low power view of lesion showing thickened rete Malpighii and characteristic cell changes ($\times 200$).

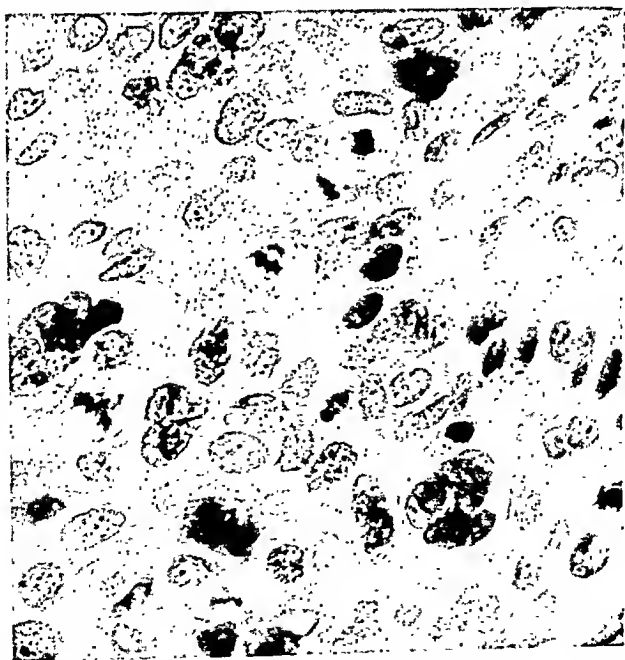


Fig. 3.—(Case No. 3.) High power view showing loss of stratification, nuclear clumping and mitoses ($\times 600$).

Pathology No. 14923 and 14977 revealed the typical histopathology of Bowen's disease. (Figs. 2 and 3.)

Case 4.—Unit No. 608321. A 54-year-old white woman was first seen in the gynecologic clinic in September, 1942, because of pruritus vulvae and ulcers of the labia. She had been treated in the dermatological clinic since March, 1942, because of a four-plus Wassermann and for verruca acuminata vulvae. Six hundred r. were given for lesions which finally were desiccated and treated with silver nitrate.



Fig. 4.—(Case No. 4.) Lower power view of lesion showing adjacent normal epithelium merging with typical Bowen's disease ($\times 200$).

She presented a typical leucoplakia and kraurosis with several discrete, papulosquamous, scaly, red lesions on the labia. No lymph nodes were felt. In December, 1942, a partial vulvectomy was performed. Since operation she has been free of symptoms and there is no evidence of recurrence.

Pathology No. 18616 revealed the typical lesion described by Bowen. (Fig. 4.)

Case 5.—Unit No. 548679. The patient, aged 69, had a "cauliflower cancer" removed from the urethra in 1924. She also had a bilateral inguinal dissection at that time and was given x-ray therapy. Details of this are not available.

She presented herself for examination because of a small ulcer on right labium minus. Multiple telangectases were noted. The duration of the lesion and symptoms are not stated. The description stated that the ulcer appeared red, eroded, encrusted, without local induration. No inguinal nodes were palpable.

The tumor and adjacent normal skin were excised. She was given 3,900 r. of x-ray therapy.

Follow-up March 20, 1943, revealed no evidence of recurrence.

Pathology No. 12467. Microscopic sections of tissue reveal typical Bowen's disease.

Case 6.—Unit No. 663398. A 64-year-old white woman, para i, gravida iii, was admitted to Sloane Hospital on January 6, 1942, because of "mass between legs" for five years. This has gradually increased in size over a period of five years with rapid recent growth.

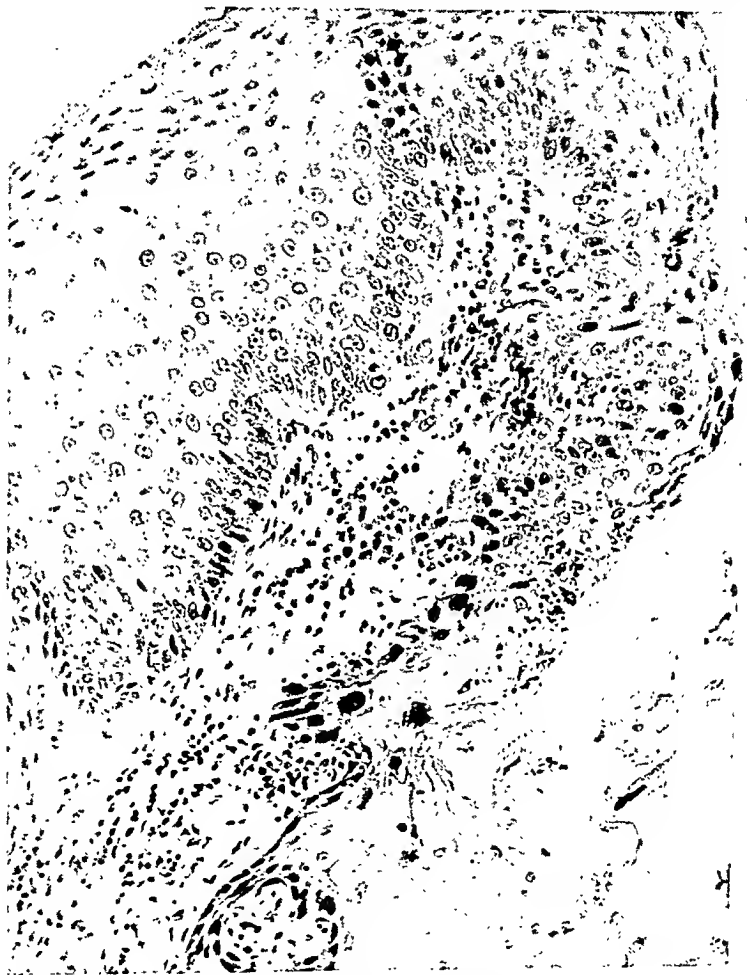


Fig. 5.—(Case No. 6.) Low power view of junction of Bowen's disease with squamous cell epithelioma (X300).

On examination a 5 cm. cauliflower mass was found involving the left labium. A few small, discrete, firm inguinal nodes were palpable.

On January 13, 1942, patient had a vulvectomy and bilateral inguinal dissection.

The patient died on twenty-fourth day postoperative from a pulmonary embolus.

Pathology No. 17383. Microscopic sections of tumor and adjacent skin revealed a typical squamous cell carcinoma. At margin of lesion, the squamous epithelium showed typical Bowen's disease, merging abruptly with epithelioma. Bowen's disease was also found in tissue

removed from right labium. The lymph nodes removed from inguinal region were free of metastases. (Fig. 5.)

Table II lists the six cases in this series for comparison with those cases reported in the literature.

TABLE II. AUTHOR'S CASES

NO.	AGE	LOCUS	DURATION	SYMPTOMS	APPEARANCE	THERAPY	RECURRENT
1	37	Fourchette	9 Mo.	Pruritus	"Encrusted Ulceration"	Excision	None
2	45	Fourchette	2 Wk.	Pruritus	Leucoplakia	Excision	None
3	35	Right Labium Majus	Several months	Pruritus	Typical	Excision	None
4	54	Both Labia Majora and Minora	Several months	Pruritus	Typical with Ulceration	Vulvectomy, Antiluetic	None
5	69	Right Labium Minus	Unknown	Not Stated	"Ulcer"	Excision, Radiation	None
6	64	Left Labium Minus Right Labia	5 Yr.	Discomfort	Typical with Ulceration and Epithelioma	Vulvectomy	Patient Died

Discussion

The age incidence of the six cases of Bowen's disease was 35 to 69 years with an average of 50.7 years. The commonest symptom was pruritus, this occurring in 66 per cent. The duration of symptoms, where stated, varied from two weeks to six years. These figures agree with previously reported cases, except for a somewhat shorter duration of symptoms.

Bowen's disease involving mucous membranes has repeatedly been shown to be more malignant than the skin lesions. Bowen's original cases, both skin lesions, ran a course over a period of many years. When the disease involves a mucosal surface, a more rapid course may be expected and local lymph node metastases duplicating the original lesion, even without demonstrable involvement of the basement membrane on serial section, may occur.³¹

Not infrequently, a Bowenoid type of epithelioma tending toward a squamous cell type develops.^{6, 24, 31} Case 6 presented such a lesion which involved the vulva. This is the only one of these cases which was associated with a typical epithelioma.

The association of Bowen's disease of the vulva with leucoplakia and kraurosis is not infrequently noted.^{4, 9, 24, 34} In this series, a definite leucoplakia was described but twice (Cases 2 and 4).

The possible etiologic role of arsenic in the development of this lesion has been suggested many times.^{3, 10, 12, 24, 35} Only one of the cases in this series had received antiluetic therapy (Case 5). None of the other cases received any arsenic locally or parenterally. Although arsenic is one of the carcinogenic agents, its role as an etiologic agent in Bowen's disease is not clear at the present time.

In every instance, treatment consisted of local excision or vulvectomy. Only one case received, in addition, 3,900 r. of radiation; this was Case

5. All the patients but one are alive, well and free of recurrence or metastases. The exact details of treatment in the cases reported in the literature are not always obvious. In several of the cases treated by roentgenotherapy or radium, the lesions recurred or spread more rapidly. It has been the experience of the departments of surgery and dermatology at the Presbyterian Hospital that excision is the therapy of choice when possible.

Over a period of twenty years, considerable discussion has arisen as to the nature of Bowen's disease. Darier³ classified the lesion as one of the "dyskeratoses." It was not long before the term "precancerosis" was applied to this lesion. Many opinions by many authorities have been expressed since 1912.^{31, 35, 38} The commonest points of difference in opinion center about the advisability of classifying the lesion as a "precancerous dyskeratosis," an ordinary epithelioma, or a specific epithelial neoplasm. As the frequency of case reports increases it becomes increasingly evident, from studying the follow-up reports, that clinically the lesion behaves like a slowly progressing superficial epithelioma. Careful study of the histopathology reveals highly specific cell alterations which are not characteristic of the usual epitheliomata. It would seem, therefore, advisable to retain Bowen's disease as a specific type of intraepithelial epithelioma running a characteristically prolonged course, presenting characteristic symptomatology and special gross and microscopic pathology. The term "precancerous" can hold little meaning inasmuch as we do not know what "precancer" looks like in any tissue. From the practical standpoint of therapeutics, a lesion must be treated either as malignant or nonmalignant.

Inasmuch as many observers do not consider Bowen's disease a distinct entity and classify the lesion with all other types of superficial intraepithelial epitheliomata, it seems advisable to emphasize again the outstanding points in the histopathology of this lesion. It is undeniable that in many instances common types of noninvasive epithelial lesions bear a superficial resemblance to Bowen's disease, from the gross appearance of the lesions, the histopathology and the clinical course. However, this resemblance is superficial. The most important means of differentiating these lesions is by careful microscopic study. Bowen's lesions present certain clear-cut cytological alterations, which, when found together make up a characteristic pattern which is not seen in the commoner types of epithelial neoplasms. Any one of these cytological changes when seen alone in a lesion, as they often are, does not make the diagnosis of Bowen's disease. The important and characteristic criteria for the diagnosis of Bowen's disease are emphasized again and include the following findings:

- (a) Hyperkeratosis and parakeratosis.
- (b) Acanthosis with marked thickening of the rete Malpighii which appear club shaped.

- (c) Loss of stratification of the individual cells; complete disorientation of the individual cells commencing just above the basal cell layer and extending to the surface.
- (d) The presence of nuclear clumping, "corps rondes," nuclear "grains" and mitotic figures.
- (e) An intact basement membrane.
- (f) Marked vascularity of the subpapillary zone with round-cell infiltration.

Not infrequently it may be necessary to cut many sections and even make serial sections of the block before all these features can clearly be identified in individual fields.

There are no cases of Bowen's disease of the vagina or cervix on file in the department of pathology at The Sloane Hospital for Women. A survey of the literature has not yielded any cases reported involving these sites. Lesions of cervical polyps, to be described in another communication, superficially resembled Bowen's disease but did not present, on serial sectioning, all the necessary criteria.

A recent report of Bowen's disease by Lampe^{29, 32} is of interest because of his unconventional method of studying the lesion. Serial sections were made in the horizontal plane rather than the usual vertical plane. By this technique, he demonstrates clearly the lateral spread of the lesion.

Conclusions

1. Bowen's disease is a specific entity, namely, a superficial, noninvasive intraepithelial epithelioma characterized by

(a) Chronicity, pruritus and a characteristic gross and microscopic appearance.

(b) More malignant tendencies when involving mucosal surfaces.

2. The therapy of choice is local wide excision.

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THE TREATMENT OF PLACENTA PREVIA, BAGGING VERSUS CESAREAN SECTION

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DURING the past two decades there has been a constant and significant decline in maternal mortality from placenta previa. Attempts to analyze this trend by large surveys of the world literature have repeatedly pointed to the increasing use of cesarean section as the major factor in this progress.^{10, 4, 7, 11} Many other factors play a role, of course, including increased recognition of the need for immediate hospitalization of these patients, and greater ease of transfusion. It is interesting to note, however, that even with these aids the maternal mortality in placenta previas delivered by the vaginal route has not dropped to a great extent.¹⁰ It appears likely that the transfusion factor is a greater aid to abdominal delivery than to vaginal delivery in this condition, for the cesarean section offers immediate termination of labor without further trauma to the cervix and opportunity to deal with the dangerous third stage under direct vision. Further loss of blood is, therefore, minimized.

Little doubt remains that cesarean section in placenta previa is safer for the baby, even for the premature one. This important consideration in treatment is now generally recognized. The realization that

abdominal delivery in the graver forms of this condition may also be safer for the mother has been more slowly appreciated. The statistical analysis of Watson and Miller in Edinburgh¹⁴ in 1925, clearly demonstrated that the best results for both mother and baby were obtained by two forms of treatment: (a) the ultraconservative, simple rupture of the membranes; (b) cesarean section, the so-called radical treatment. They found that disastrous results most often attended the "intermediate" forms of treatment, such as bagging and version. In recent years many writers in this country have re-affirmed the unquestionable value of cesarean section in treating placenta previa.^{9, 3, 8, 11, 6, 12} Yet there is still detectable in the literature a reluctance to recognize cesarean section as a safe and really conservative treatment of this condition in its more severe forms.

At the Sloane Hospital for Women there has been a definite trend in recent years toward the treatment of the graver forms of placenta previa by cesarean section. We have undertaken a study of this trend in order to define the merits of our various modes of treatment and, particularly, to ascertain the reason for the markedly diminished use of the hydrostatic bag. Restricted use of this latter technique would seem particularly significant in an institution where the Voorhees bag has been widely and, therefore, probably skilfully used in the past.

We have studied seventy-six cases of placenta previa treated at the Sloane Hospital during the past ten years. This group includes only cases where the placenta was definitely palpable on pelvic examination or proved low at cesarean section. It excludes those cases where the presumptive diagnosis of low implantation was made, for they are usually neither susceptible of definite proof nor in need of any special treatment. This choice of cases of necessity makes for a less optimistic statistical result, but places the problem of treatment properly in the group of cases that requires it.

The group includes nineteen cases of central placenta previa, nineteen cases of partial placenta previa, and thirty-eight cases of marginal placenta previa. In tabulating the results of treatment we have aimed principally at a demonstration of the relative efficiency of bagging and cesarean section, these being the most frequent forms of treatment in the cases which required more than simple artificial rupture of the membranes.

TABLE I. RESULTS OF TREATMENT IN PLACENTA PREVIA

Fetal mortality is corrected to exclude babies under twenty-eight weeks and those with no fetal heart on admission.

Shock, hemorrhage, and morbidity figures are corrected for cases where such factors were present before treatment was instituted.

	NO. OF CASES	FETAL MORTALITY	MATERNAL MORTALITY	SHOCK	HEMOR- RHAGE	MORBIDITY
Cesarean Section	29	11.1%	3.4%	10.3%	13.7%	37.9%
Bagging	26	50.0%	11.5%	61.5%	46.1%	57.6%

These results indicate the marked advantages of cesarean section over bagging for both mother and baby. There was but one death following section and this one had been treated unsuccessfully with bagging prior to operation. In breaking the figures down further for evaluation of individual surgical factors, the cesarean section group showed a much smaller incidence of shock and hemorrhage than did the bagged cases, and moderately less morbidity. The "radical" nature of abdominal delivery in the treatment of placenta previa is not apparent from these figures. Its efficiency is notable in the face of the disastrous incidence of shock and hemorrhage in bagging as typified in the following case:

Mrs. S. L., a twenty-seven year old, para i, gravida ii, entered the hospital on September 18, 1942, approximately two weeks before term, with a history of rather profuse, painless, vaginal bleeding shortly before admission. On entry to the labor room, since no further bleeding was noted, patient was sedated mildly, kept flat in bed, and vaginal examination deferred. There was no bleeding during patient's next four days on the ward.

On September 22, 1942, the patient was returned to the delivery room for diagnostic vaginal examination. At this time the placental edge was palpable, partially covering the internal os, and the cervix was found to be one-and-one-half fingerbreadths dilated and partially effaced. Since the bleeding was not alarming, the patient in good condition, and pelvic delivery deemed preferable, it was decided to await the onset of labor. During the next twenty-four hours bleeding was mild and intermittent but labor did not supervene.

On September 23, 1942, vaginal examination was repeated, therefore, and the cervix was then found almost two fingerbreadths dilated and completely effaced. It was firm and of moderate thickness. The placenta could now be more definitely delineated and it was found to cover a great portion of the cervical os. The success of several attempts at artificial rupture of the membranes could not be evaluated due to bleeding. A #3 Voorhees bag was introduced in extraovular fashion. During this procedure the patient lost approximately 400 c.c. of blood and at its termination the fetal heart could not be heard. There were some irregular contractions and a small amount of bleeding during the next twenty-four hours.

On the following day, September 24, 1942, the bag came out, but bleeding was minimal, labor insignificant, and no vaginal examination was made. The patient was transfused and given mild sedation with marked benefit to her general condition.

In the next twenty-four-hour period there was no bleeding of note but the patient became markedly febrile, her temperature rising abruptly to 104° F. She was, therefore, taken to the delivery room on September 25, 1942, and transfusion started. She was then prepared for delivery, and vaginal examination revealed a rather elastic cervix, three-fingers dilatation. The membranes were artificially ruptured, the cervix manually dilated with ease, and internal version readily effected. Slow extraction of the macerated fetus followed. The placenta did not separate readily so a manual removal was deemed advisable. This was done and the uterine contents packed. Inspection of the cervix revealed no laceration.

Hemorrhage was brisk during most of the operation and was estimated at 800 to 1,000 c.c. Shortly after the end of the procedure the temperature rose precipitously to 106° F. with a shaking chill. The patient became markedly cyanosed thereafter with pulse rapid and thready. The blood pressure dropped to marked shock levels. With oxygen, repeated transfusion of whole blood and plasma, saline infusions, shock position and supportive measures, the patient's condition gradually improved over a period of twenty-four hours.

The post-partum course was moderately febrile for five days and marked by a pulmonary process, embolic or bronchopneumonic in character. This was treated with chemotherapy and a supportive regime to which the patient readily responded. She was discharged well on the fourteenth post-partum day.

In going into the merits of bagging, both intraovular and extraovular, we found it successful in controlling bleeding and initiating satisfactory labor in only 19.2 per cent of the cases. Furthermore the problem did not end with the success of the bagging, for a serious operative delivery was necessary in 69.2 per cent of the bagged cases. Bleeding frequently recurred when the bag was expelled with the cervix still incompletely dilated. Further operative procedures then became necessary, version and extraction being the one most frequently employed. These considerations must be borne in mind when one evaluates bagging and pelvic delivery as a conservative measure. One must compare cesarean section with a technically difficult, hazardous set of major obstetric procedures through an area which is the site of the obstetric abnormality. And in thinking of the future childbearing career of any individual patient, the possible sequelae of difficult pelvic delivery—cervical lacerations, pelvic floor lacerations and relaxation of the pelvic fascial supports—complications which occur in a significant percentage of cases, must be balanced against the chance of a repeat cesarean section.

Even the most serious forms of placenta previa, the cases with marked hemorrhage and shock on admission to the hospital, have in our experience responded better to abdominal delivery following transfusion and supportive treatment. We reviewed five such cases in our study; only two emerged from delivery in good condition and these had been treated by cesarean section. A tabulation of our fatal cases is also interesting in that it further emphasizes the danger of pelvic procedures in placenta previa:

Our small group of placenta previas, delivered operatively through the pelvis without bagging, showed a similarly high incidence of shock, hemorrhage, and other complications. Their outcome contrasted sharply with the much more favorable results in spontaneous pelvic delivery or abdominal delivery.

We do not desire to urge cesarean section as a universal treatment for placenta previa. Each case must be considered individually and many cases can be successfully treated by simple artificial rupture of

the membranes. When such treatment is contemplated obstetrical judgment must be used in the evaluation of (a) the condition of the cervix; (b) the quantity of the bleeding; (c) the irritability of the uterus or the quality of the labor; (d) the type of previa. The condition of the cervix is the most important factor, for on it depends the time which must elapse before delivery can be anticipated by the pelvic route.

TABLE II. DEATHS FOLLOWING TREATMENT

CONDITION BEFORE TREATMENT	TREATMENT	COMPLICATION	RESULT
(1) Marked Hemorrhage Shock	B. H. Version and Ex- traction	Increased Hemorrhage and Shock Cervical Laceration	Death
(2) Shock	Bagging (Unsuccess- ful) Followed by Section	Shock Endometritis Peritonitis Pneumonia Congenital Heart Disease	Death
(3) Moderate Hemorrhage	Bagging Pituitrin	Shock Hemorrhage Endometritis Septicemia Cervical Laceration	Death
(4) Mild Hemorrhage	Manual Dilatation Breech Extraction	Hemorrhage Shock	Death
(5) Brisk Hemorrhage	Bagging B. H. Version and Ex- traction	Hemorrhage Shock Endometritis Parametritis Peritonitis Cervical Laceration	Death

Our figures bear out the efficacy and safety of simple rupture of the membranes when used in the proper cases. Of twelve cases of marginal previa where this procedure was used as a specific therapy, it successfully controlled hemorrhage and was followed by spontaneous delivery in eleven. One case was only moderately successful in that operative pelvic delivery was necessary.

In contradistinction to these results, bagging was moderately successful in two of eight marginal placenta previas in which it was used:

TABLE III. MARGINAL PLACENTAL PREVIA, COMPARISON OF RESULTS FOLLOWING RUPTURE OF MEMBRANES AND BAGGING

	NO. OF CASES	FETAL MORTALITY	MATERNAL MORTALITY	SHOCK	HEMORRHAGE	MORBIDITY
Artificial Rupture of Membranes	12	16.6%	0	0	0	8.3%
Bagging	8	25.0%	25.0%	62.5%	37.5%	50.0%

the bleeding was controlled to a fair degree and spontaneous delivery occurred. The other six cases were failures, for they were marked by uncontrolled bleeding, serious operative delivery or both.

When a diagnosis of placenta previa has been made and the child is still quite premature we feel justified in waiting if the following conditions are fulfilled: (a) the patient can be kept in bed in the hospital; (b) hemorrhage ceases with bed rest; (c) little or no bleeding is evoked by gentle vaginal examination; (d) patient's general condition is good.

Summary and Conclusions

1. We find two efficient methods of treating placenta previa: (a) simple artificial rupture of the membranes; (b) cesarean section.

In the milder forms of this condition the former can be used widely and effectively.

2. The use of the Voorhees Bag in the treatment of placenta previa is dangerous and inefficient. It should be avoided.

3. In deciding treatment, the state of the cervix and the quantity of bleeding at examination are most important considerations.

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THE VALUE OF MIXED CONJUGATED ESTROGENS FROM PREGNANT MARE'S URINE IN THE TREATMENT OF MENOPAUSE*

A Preliminary Report†

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THE clinical application of hormones for the prevention and control of the menopausal syndrome has been the subject of many communications. Since the clinical manifestations, in this period of transition, have been primarily attributed to a gradual or sudden cessation of ovarian function, the use of estrogenic substances for their alleviation seemed logical. In addition, disturbed metabolic processes become evident at the same time and consequently the final chapter regarding the treatment of the climacteric has not yet been written. Present day methods of bio-assay make it possible to determine the biologic potency of hormone therapy, something that was not feasible until recent years. Supplementing this, newer advances in biologic chemistry have provided methods of isolating and synthesizing the true estrogenic hormones which are steroid compounds. The approach to the solution of the symptomatic problem has been through either parenteral, or oral therapy, or a combination of the two.

During the past few years a new nonsteroid compound, stilbestrol, possessing estrogenic activity, has been widely used. Although quite potent when administered orally, this substance produces toxic side effects in about 15 per cent of patients. Since such a chemical substance is toxic to a certain degree, it is possible that its prolonged use may eventually produce pathologic alterations not yet recognized, although reports of skin lesions and other manifestations are beginning to appear in the literature.¹ The only real advantage of stilbestrol over the steroid compounds is its low cost.

Ever since they have been available, the steroids have proved satisfactory, particularly when given parenterally. By the oral route, much larger amounts are required to be effective.² This is due to their destruction in the gastrointestinal tract, liver inactivation and low solubility in water, so that most of the hormone is not utilized.

For the past year we have been experimenting with a water-soluble, orally active preparation of the estrogens derived from pregnant mare's

*This preparation is marketed under the trade name of Premarin, manufactured by Ayerst, McKenna and Harrison, Ltd., Montreal, Canada.

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urine. The predominating component is estrone sulfate, although presumably smaller amounts of equelin and other estrogens in mare's urine are also present. The product is standardized by both chemical colorimetric and biologic assays. Each tablet contains 1.25 mg. of the mixed conjugated estrogens of pregnant mare's urine expressed in terms of the principal component, sodium estrone sulfate.

Method

This study is based on observations in sixty-one women, eight of whom did not return for a proper follow-up, leaving fifty-three from which to draw conclusions. The age range was from 32 to 55 years and none of the cases were selected. The usual variety of symptoms were present, i.e., hot flushes fifty-nine, dizziness twenty, headaches sixteen, perspiration and sleeplessness twenty-one, nervousness ten, weakness eight, nausea five, melancholia two, fatigue three, backache two, numbness one, fainting one, lower abdominal pain one. There were eleven instances of artificial menopause and forty-two of natural menopause, the former group presenting the more severe symptoms. Twelve patients were still menstruating, some irregularly. Repeated vaginal smears, stained according to a technique developed in our laboratory,³ were taken from all patients before the onset and during treatment. Observation and treatment of this group ranged from four weeks to one year.

All patients received three tablets daily until all flushes were completely under control. The maintenance dosage was then calculated clinically, i.e., the smallest daily dose required to keep the patient symptom-free. Treatment was discontinued during menstruation or when periods of bleeding occurred. Most of the patients were seen at weekly intervals for the first month, then at increasing intervals thereafter.

Results

Complete control of flushes varied from two days to five weeks in all patients who followed instructions and reported regularly. The average time required for alleviation of symptoms was ten days. In addition, appetite increased, sleep improved, attacks of perspiration disappeared, and there was definite improvement insofar as other complaints were concerned. All patients described a sense of well-being. Symptoms returned when medication was discontinued without permission, although the flushes were not as frequent or severe. Immediate return to hormonal therapy controlled the symptoms within a short space of time. With the exception of two patients, all tolerated the preparation well.

Bleeding appeared in five patients lasting 5, 8, 11, 14 and 21 days respectively. During this time they were advised to discontinue the hormone. No medication was prescribed for the bleeding itself.

Several women complained of increased vaginal secretion, but not to the point of discomfort.

Vaginal smears taken before organotherapy was begun showed various pictures, ranging from that of mild menopause changes (slight cornification, superficial and intermediate cells predominating) to one of a severe menopause (many deep cells, superficial cells, leucocytes and bacteria).

Discussion

To imitate normal human endocrine physiology, orally active biologic extracts are necessary to maintain a constant hormone level. At the present time, both estrin and progestin are available in this form, yet their use does not entirely solve the many problems which confront us in the field of gynecologic endocrinology. It will be far better when orally active endoerines which can stimulate either the pituitary or the ovaries, so that the individual can produce her own estrin and progestin, are available. In the climacteric, however, these theoretically ideal gonadal activators would not be of any particular value. This seems to be factual, since progressive sclerosis of the ovaries renders them incapable of responding to stimulation by the normal or even excessive gonadotropic hormones of the pituitary. Effective pituitary stimulation of the ovary is therefore predicated on the state of responsiveness of the ovary.

The next best approach then is substitution therapy. This method of treatment has been in vogue for many years with the use of desiccated extracts which were relatively biologically inert, and the need for more potent organotherapeutic agents is evident. The three estrogens which are present in the human are estradiol, estriol and estrone. The first is considered to be the true follicular hormone and is the most potent of the three. The others are metabolic products of estradiol. All have been in wide use orally but not in conjugated form. They are effective only in large doses and their chief disadvantage has been their high cost. The use of stilbestrol, although potent in estrogenic activity and low in price, is not always feasible, since it so often initiates nausea and vomiting and sometimes abdominal pain.

The extracts under consideration in this investigation are derived from pregnant mare's urine and maintained in the conjugated form in which they are excreted, probably as sulfates. The preparation is not chemically pure estrone sulfate, since other fractions are brought down with it. It has the signal advantage over the nonconjugated steroids in being water-soluble, assuring a rather rapid rate of absorption from the gastrointestinal tract. It seems highly potent, since all of my patients were

Plate 1. Patient S. V., aged 33 years. Severe menopausal symptoms; vaginal smear, atrophic, showing many deep cells and leucocytes. Estrone sulfate (1 tablet t. i. d.) was administered.

Plate 2. Patient S. V., after seven days of medication. Vaginal smear shows presence of cornified cells, intermediate cells and some superficial cells; good estrogenic activity. Hot flashes were completely under control.

Plate 3. Patient R. de S., aged 41 years. Severe menopausal symptoms; vaginal smear atrophic, showing superficial cells, many deep cells and leucocytes. Estrone sulfate (1 tablet t. i. d.) was administered.

Plate 4. Patient R. de S., after seven days of medication. Vaginal smear shows complete cornification; excellent estrogenic activity. Hot flashes were completely under control.

Plate 5. Patient T. F., aged 51 years. Moderate menopausal symptoms; vaginal smear was not atrophic, showing superficial cells and debris. Estrone sulfate (1 tablet t. i. d.) was administered.

Plate 6. Patient T. F., after seven days of medication. Vaginal smear shows only a slight change; poor tissue response to the estrogen yet hot flashes were completely under control.

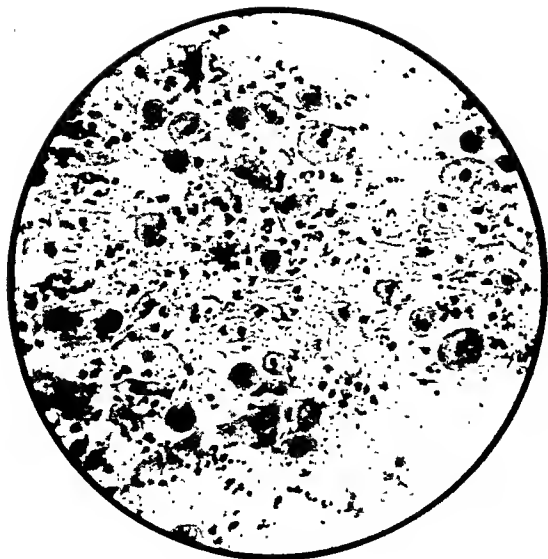


Plate 1



Plate 2

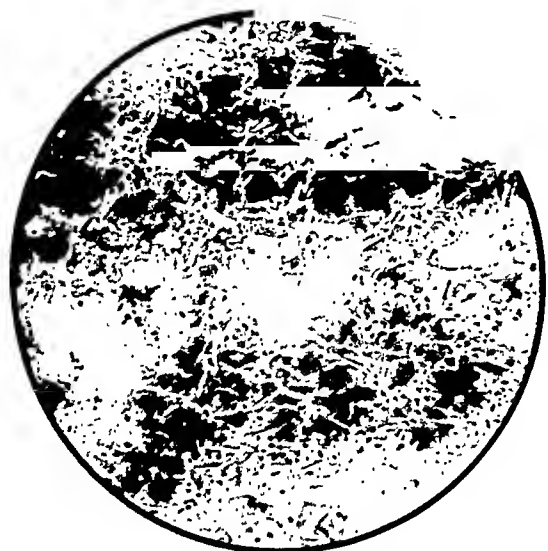


Plate 3

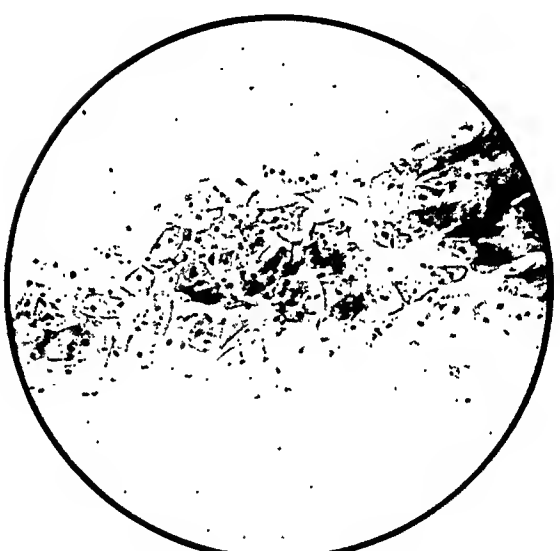


Plate 4

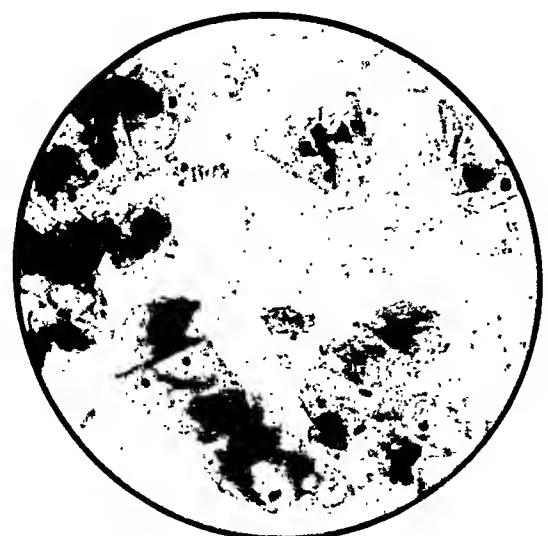


Plate 5

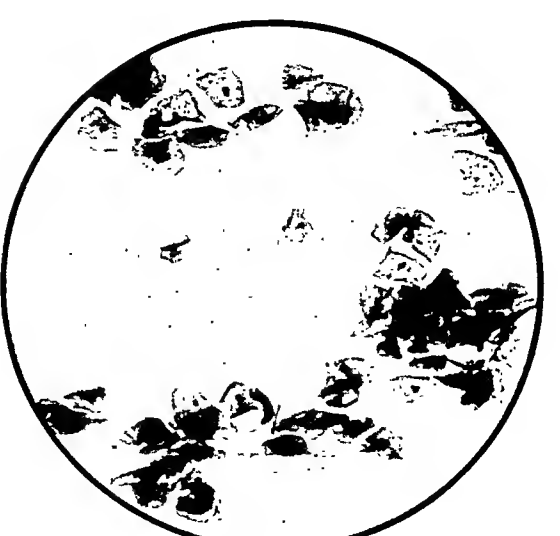


Plate 6

materially benefited. In the two instances in which the hormone was not tolerated, one patient suffered from nausea and vomiting previous to treatment and the other patient, a surgical castrate, was so emotionally unstable that even other medications were of no value. The maintenance dose varied from one tablet daily, to two tablets alternating with one tablet every other day. Some individuals who improved rapidly discontinued treatment themselves, but within two to three weeks the flushes reappeared, although not as frequently or as severe. Restoration of therapy controlled the symptoms again in 3 to 4 days, and most patients immediately felt much better. The beneficial effect on libido was rather striking in some instances.

The periods of bleeding which appeared in five cases cannot fairly be ascribed to the hormonal withdrawal, since they occurred during the course of treatment. Discontinuance of the medication was advised but no treatment was instituted insofar as the bleeding was concerned. Vaginal smears which at first varied from mild to severe changes, usually became highly cornified with the elimination of cellular debris within seven days (Plates 1, 2, 3, 4). In some instances the effects on the vaginal epithelium were slow, even though the patient showed rapid clinical improvement (Plates 5, 6). It soon became obvious that clinical improvement did not always parallel the smear changes. Probably if larger doses, which seem to be unnecessary for symptomatic relief, were used, all smears would show a high type of cornification. The increased vaginal secretion evidenced by some individuals is apparently due to excessive maturing and cornification of vaginal epithelium which is a specific effect of the hormone used.

My acknowledgment is extended to Dr. W. T. Dannreuther for his constructive criticism and helpful cooperation.

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27 EAST 93RD STREET

A CLINICAL AND LABORATORY STUDY OF THE SYNTHETIC ESTROGENIC SUBSTANCE, OCTOFOLLIN

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THE discovery of the estrogenic activity of the synthetic compound diethylstilbestrol by Dodds and his co-workers¹ was a great step forward in the simplification of hormone therapy in gynecological practice. There is no doubt that diethylstilbestrol and its derivatives are clinically effective. However, toxicities, varying in frequency and intensity, have been reported by practically all investigators studying the effect of the drug in non-puerperal women. Morrell² and the Council on Pharmacy and Chemistry³ have recently reviewed this literature.

It is to be expected that under the conditions outlined above an effort would be made by various research organizations to develop new compounds which might retain the orally active estrogenic potency of diethylstilbestrol but exhibit no, or greatly decreased, toxicity. It is the result of a clinical and laboratory study upon one such synthetic estrogenic compound that we wish to report here.

This compound was originally designated as, "118 B," but has been given the name, Octofollin.* The researches leading to the development of this substance have been outlined by Blanchard, Stuart and Tallman.⁴

Our clinical study of this compound can be divided into two phases. The first project was concerned with the determination of the clinical effectiveness of the drug, and the second was a detailed study of the reactions of a group of hospitalized patients to large overdoses of octofollin.

Clinical Studies

We began to use octofollin in the gynecologic endocrine clinic of Bellevue Hospital in October, 1941. As no clinical work had been reported at that time our information was very meager, and the drug was started in $\frac{1}{2}$ mg. daily doses. The patients were seen every week and closely questioned as to their menopausal status and possible toxic reactions. Many of the older patients in the clinic refused to be changed from their injections to the new tablets, and their influence upon the experimental group, together with our constant and over-enthusiastic search for toxic reactions, resulted in rather disappointing results at first. For example: in the first three months of the work we gave the drug to 70 women, with successful results in only

*Octofollin was developed in the Research Laboratories of Schieffelin & Co., New York City, and we wish to express our appreciation to Dr. E. W. Blanchard, and Mr. A. R. Meares of that organization for their cooperation in this study.

33. Two of the group in whom oral treatment was unsuccessful obtained complete relief of symptoms following the administration of octofollin in oil by intramuscular injection.

Gradually the dosage was increased to about 2 mg. per day. At this time the first clinical report of the Chicago group appeared, and one of our patients, misinterpreting our directions, took 2 mg. t.i.d., had no toxic symptoms, and obtained relief symptoms. Since then, more of the drug was used, both in daily dosage and number of patients treated. In the following five months' period 25 menopausal patients were started on 5 mg. per day, and 17 reported relief of symptoms with no side reactions. Two others of the group were successfully treated with the drug by injection.

During the first year that accurate records were kept, octofollin was given to 131 patients (105 natural menopause, 12 surgical menopause, 3 x-ray menopause, and 11 miscellaneous). Since this group contains our early cases—which we now know received insufficient dosage—a statement as to the percentage of satisfactory results would hardly be accurate. It may be of more significance to state that at the present time we are running a weekly clinic of about 35 patients—mostly menopausal—with 77 per cent receiving octofollin, and the remainder natural estrogen by injection. No patients have been taken off the drug because of toxic symptoms in the last nine months. At the present time all our menopause patients are started on 5 to 10 mg. of octofollin per day by mouth and the dosage gradually changed according to their clinical progress. Those patients who report little relief from the tablets, or who have overwhelming preference for injections, are given octofollin in oil, 2 to 5 mg. intramuscularly one to three times a week. The use of the synthetic estrogen has helped to a great degree in decreasing the weekly clinic load, inasmuch as those patients receiving their medication orally attend the clinic but once every two to three months. Since these patients do not come in to the clinic except to receive a new supply of tablets, it can safely be assumed that they are obtaining satisfactory relief, and that no toxicity has occurred. This assumption is substantiated by their reports to the doctor in charge.

From our experience with this new synthetic estrogen it would seem that it is an effective agent with a minimum amount of "toxicity" at the therapeutic levels. Our conclusions do not agree with the Chicago group, however, in the dosages found to be effective. In our hands the average effective oral dose is between 1.0 and 5.0 mg. with several patients taking 10 mg. per day.

Laboratory Studies

In March, 1942, it was made possible for us to undertake a rather intensive study of the effect of large doses of octofollin as reflected in possible changes in blood, urine, liver function, and clinical reactions. It was obvious that the clinic group was unsatisfactory for such a constant laboratory study, and therefore the drug was tested on a care-

fully selected group of hospitalized patients. From March 5, 1942, all patients in the gynecologic service of Bellevue Hospital who satisfied the following requirements were used as test subjects:

1. Those patients who had been subjected to surgery at which time a bilateral oophorectomy or, in case of previous surgery, the complete removal of any remaining ovarian tissue had been performed.
2. Those patients who had never complained of any hypo-ovarian or menopausal symptoms in their preoperative state.
3. Those patients who on the third day of their postoperative course were afebrile or closely approached that state, and presented no intestinal or peritoneal disturbances which might confuse the interpretation of our results.

In this study of six months' time, 23 patients have satisfied the above requirements. The essential data on these women are given in Table I.

TABLE I. ESSENTIAL DATA ON PATIENTS RECEIVING OCTOFOLLIN POSTOPERATIVELY AND BEING STUDIED BY ANALYSES AND CLINICAL EXAMINATIONS

RACIAL DISTRIBUTION: WHITE, 9; NEGRO, 14		
AGE DISTRIBUTION:		
21 to 30 years	31 to 40 years	41 to 50 years
7	11	5
OPERATIVE DIAGNOSIS:		
Uterine fibroids and chronic adnexal disease		14
Uterine fibroids and cystic ovary (or ovaries)		2
Uterine fibroids		3
Chronic adnexal disease		3
Ovarian cysts		1
OPERATIVE PROCEDURES:		
Supracervical hysterectomy and bilateral salpingo-oophorectomy		17
Supracervical hysterectomy and unilateral salpingo-oophorectomy		3
Total abdominal hysterectomy and bilateral salpingo-oophorectomy		1
Bilateral salpingo-oophorectomy		1
Bilateral oophorectomy		1
ASSOCIATED DISEASES:		
Essential vascular hypertension		3
Chronic diffuse glomerulonephritis		1
Syphilis		3
Obesity		2
Secondary anemia		4

All patients under study were handled in a uniform manner by one observer. On the third or fourth postoperative day, a complete blood and urine analysis, blood pressure, icteric index, and clinical examination were performed. The first patients of the series were then given 5 mg. of Octofollin for the rest of their hospital stay. At regular intervals during their hospitalization, analyses and examinations were repeated. As the study continued the dosage increased until we were finally giving a total daily dosage of 30 mg. (10 mg. t.i.d.). On discharge from the hospital the patients were given an adequate supply of the drug to maintain their high dosage for varying periods of time. The amount of the drug taken varies with the duration of the observations; as much as 990 mg. have been given in 33 days. Upon their return to the clinic, analyses and examinations were again performed. Subsequently, several of the patients were taken off the drug to ascertain the character and degree of the withdrawal symptoms following the cessation of the estrogen supply. The therapeutic value was again tested by adding the drug to their daily regime.

Two patients died within four days of their operation, from causes unassociated with the administration of the drug, as confirmed by post-mortem examination. The remaining 21 patients were seen throughout their entire hospital stay and 16 were again seen at the clinic for varying periods of time. The earliest cases have been followed for seven months.

The total amount of drug taken by the individual patients varied greatly, depending upon the initial dosage, the length of time under observation and the results of the clinical examinations. All cases received far greater amounts than the therapeutic dose as reported by the Chicago workers and indicated above by us.

Results

Preliminary data, prior to the administration of octofollin, showed fairly normal distribution of findings. The white cell counts varied from 6,900 to 18,650. The red cell counts showed either a moderate anemia or a normal range, with the hemoglobin closely correlated to the cell counts. The differential count revealed a fairly high polymorphonuclear cell value, with increased immature forms, and a correspondingly low lymphocyte count. No case presented an abnormal number of eosinophilic, basophilic or monocyte cells, and the red cell picture presented no gross abnormalities other than the microcytonia and hypochromia expected in the anemia cases. Urines were normal in all but the case with mild glomerulonephritis, even this showing only albumin and a normal microscopic picture. Blood pressures were normal in 19 cases; hypertension of moderate degree was present in the case of renal disease and in three instances of essential vascular disease. Icteric indices varied from 2.5 to 5.0 with no clinical jaundice appearing in any patient.

It may be stated as a general conclusion that no changes in any of the analyses occurred which would indicate the slightest degree of toxicity following the administration of octofollin. Those postoperative changes which might be expected to follow the removal of a source of infection and/or irritation in any series of postoperative patients took place in the normal manner; e.g., improvement of anemia; return to the normal type of differential count, etc.

A detailed analysis of the laboratory findings included:

A. Blood Studies:

1. *White Blood Cells.*—Under the course of administration of the varying dosages of the drug, the white cell count showed no change other than would be expected in the normal postoperative patient; the rapidity with which the count approached normal levels did not depend upon the magnitude of the dose. The lowest count found was 4,600, occurring on the seventh day of administration of 10 milligrams daily; the patient had at this time a normal differential count and no clinical symptoms referable to the lowered reading. Continued administration of octofollin was followed by normal levels.

2. *Differential Cell Count.*—From the original hyperpolymorphonuclear count found prior to the administration of 118 B, a gradual

lower level was reached, all cases approaching a normal distribution of cells on their discharge from the hospital. As both the total polymorphonuclear count and the immature cell proportions dropped, the lymphocytes rose to their normal percentage. The rate of approach to the standard was in no way dependent upon the level of drug administration. The eosinophilic, basophilic and monocytic cells remained normal at all times. The continued use of octofollin in the clinic was never followed by any more than a normal deviation of the cell distribution.

3. *Red Blood Cells*.—A small number of patients had on admission to the hospital some gynecological disease associated with excessive vaginal bleeding and a resultant secondary anemia. These patients were given, prior to surgery, varying amounts of whole blood by transfusion. Their red cell counts on the third postoperative day still revealed a moderate secondary anemia. Administration of the drug did not interfere with the gradual but steady increase of the cell count, except in two instances of transitory depression. The first occurred in a patient receiving five milligrams daily for seven days, at which time the red cell count had fallen from 4.50 million to 3.44 million and the hemoglobin from 86 per cent to 79 per cent. The second was a patient with an original count of 4.03 million on the third day and whose values fell to 3.36 and 3.22 million on the sixth and tenth postoperative days, the third and seventh days of administration of octofollin, 5 milligrams daily. At both these determinations, however, the hemoglobin continued to rise. Both cases were maintained at the same drug levels as before, and on subsequent determinations at the clinic were found to be normal in both readings.

4. *Hemoglobin*.—All readings were done by a single observer with the Sahli apparatus, 100 per cent being equal to 14.0 Gm. There were no effects other than almost a continuous rise in this value, practically all patients ending the period of observation with higher levels than at the first postoperative reading.

5. *Red Cell Appearance*.—Beyond the microcytosis and hypochromia of the secondary anemia, no abnormal findings could be observed.

6. *Icteric Indices*.—Blood drawn at varying intervals during the hospital stay and clinic visits were examined for evidence of liver dysfunction. No patient had presented any clinical evidence of jaundice or liver pathology. All determinations give values within normal limits, no degree of pathologic change being produced with the large dose of 30 milligrams a day.

B. Urine Studies:

In none of the characteristics studied (specific gravity, reaction, albumin and reducing substance content, and microscopic picture) did the urine vary from the normal, with the exception of our single patient with chronic diffuse glomerulonephritis. In this latter patient the findings were in no way changed by the administration of octofollin.

C. Blood Pressure Studies:

Four patients had elevated blood pressure readings, both pre- and postoperatively; three with essential hypertension and one with renal disease. In none of these nor in any of the remaining 17 were any significant changes observed during the entire period of study.

Clinically, the patients revealed other interesting symptoms:

A. Presence of symptoms attributed to lowered estrogenic hormone levels:

Although an occasional case of complete oöphorectomy may present the picture of sudden menopausal syndrome while in the hospital, the onset of symptoms usually occurs some time later. This fact was realized at the onset of this study and there was no attempt to use these studies to evaluate the therapeutic efficiency of the drug under consideration. It is, therefore, only as an interesting fact that we state that 5 patients, 31 per cent of those seen in the clinic, developed some menopausal complaints while still on the medication. When the individual doses in three of these cases were increased all three were either markedly or completely improved.

B. Toxic effects:

One of the original aims in producing another synthetic estrogen was to find one with less toxicity than diethylstilbestrol or hexosterol. Although our laboratory findings did not reveal any pathological findings in this study, it is not inconceivable to imagine a clinically toxic effect not reflected in the body fluids or metabolic tests. In the close observation of the twenty-one living patients only one complained of nausea and vomiting after ingestion of the drug. This case, with mild chronic glomerulonephritis, received 10 milligrams twice a day on the fourth postoperative day and subsequently until a total of 100 milligrams had been taken. During this time she complained of diffuse abdominal soreness, nausea and occasional vomiting, not associated at all with the time of drug ingestion. At this period, the temperature was normal, the abdomen obese, slightly distended and not tender. The bowels moved only with enemata. The dose of the drug was lowered to 5 milligrams twice a day and was immediately followed by complete cessation of complaints. Later, the dosage was raised to 15 milligrams daily and the patient, ambulant at this time, had no recurrence of any complaints.

No other instances of nausea or vomiting occurred. There were no cases that presented jaundice, hepatic tenderness, rash, pruritus, mental disturbances or intestinal disturbances. The only other voluntarily offered comments from the patients included a marked increase in appetite in one and a sudden increase in libido, both in the hospital and later at home, in another.

C. Clinical effects of sudden withdrawal of octofollin:

Of the 16 patients followed at the clinic, 12 were told to stop taking their medication. Two of these have not as yet returned for evaluation of their status. Of the remaining ten, 80 per cent have developed menopausal complaints of varying degree; the other 20 per cent have presented no complaints at all. In a general manner, the severity of the symptoms was correlated with the dosage of the synthetic estrogen that they were receiving immediately before the withdrawal, but the correlation is not perfect.

D. Clinical effects of reinstituting therapy with octofollin:

The eight patients who developed menopausal complaints were placed back on the drug, the dosage higher than those suggested by Freed and Greenhill, and found efficient by us. Three have still to be seen

at the clinic; the five who have been seen all present marked to complete relief.

Summary and Conclusions

1. A detailed study of the clinical effectiveness and possible toxicity of a new synthetic estrogen, octofollin, unrelated to the stilbenes, has been made.

2. In our hands it has proved to be an effective estrogen, when administered either orally or parenterally, and much less toxic than diethylstilbestrol at the therapeutic levels.

3. In the intensive study of the hospitalized and the clinic group we would conclude that the average therapeutic range, for oral therapy, is 1 to 5 mg. per day.

4. In those patients who, for various reasons, do not respond well to oral therapy complete or marked relief may be obtained by administering the drug intramuscularly in oil: 2 to 5 mg. one to three times per week.

5. Twenty-one carefully selected patients, from whom all ovarian tissue was removed, were given large overdoses of octofollin for varying times beginning on the fourth postoperative day, and a careful study was made of possible abnormal changes occurring in the blood cell picture, hemoglobin level, blood pressure, urine, and icteric index which might indicate toxic reactions to the drug. Sixteen of these patients have been followed in the gynecologic endocrine clinic following their release from the hospital—the earliest cases for 6 months. No evidence of any toxic changes was found.

6. A single case of nausea and vomiting in this postoperative group was stopped by reducing the dose to half, 20 mg. per day to 10 mg. per day. The resultant dose was still above the necessary level, and later elevation of the dosage did not bring about a recurrence of the complaints.

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AN EVALUATION OF THE LOCAL USE OF SULFONAMIDE DRUGS IN CERTAIN GYNECOLOGICAL OPERATIONS

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IN THE medical literature of the past few years, a number of reports have appeared describing the local use of powdered sulfonamide drugs in a variety of surgical procedures. These reports have been almost uniformly favorable, the striking reduction in mortality from simple or complicated acute appendicitis presenting perhaps the most outstanding proof of the efficacy of this relatively new therapeutic measure.

Lockwood,¹ in 1941, after extensive clinical and laboratory studies, laid down the principles involved in the use of sulfonamide therapy as an aid to surgery. These principles may be stated briefly as follows:

1. Sulfonamide compounds produce their results in infectious lesions by exercising a bacteriostatic effect on the organisms present.

2. This effect is probably the result of specific interference with enzymatic utilization by bacteria of some nutritive chemical factors such as para-amino-benzoic acid.

3. These substances, whose utilization by organisms has been blocked, will act also as inhibitors of sulfonamides when present in more than minimal concentrations.

4. The curative effects of sulfonamides are maximal when the concentration of drug is high, when the local cellular defense is active and when the concentration of sulfonamide inhibitors in the infected area is low.

5. Localized areas of tissue necrosis and abscess formation contain large quantities of sulfonamide inhibitors, and organisms within such lesions are protected against the effects of the drugs.

Material Reviewed

On the gynecologic service at Bellevue Hospital, during the period from June 1, 1941, to May 1, 1943, sulfonamide drugs were used locally in abdominal operations on 62 occasions. Sixteen of these cases differed so widely as to type or as to manner of use of the drugs that they were excluded from this report. In 46 instances, however, the cases could be placed in one or another of four rather distinct categories and these 46 cases have been analyzed as to indication for sulfonamides, post-operative morbidity, complications, wound healing and length of hospitalization. Similar unselected cases in which no sulfonamide drugs were employed were analyzed in the same way for purposes of comparison.

A. Complete Hysterectomy

In 13 cases, the primary indication for the use of sulfonamides was the performance of abdominal complete hysterectomy with potential

contamination of the peritoneal cavity from the vagina. Routinely, about 3 Gm. of powdered drug were placed between the leaves of the broad ligaments and beneath the anterior bladder flap of peritoneum with an additional 3 Gm. being deposited in the cul-de-sac and about the operative site. In only 4 cases was the drug also placed in the abdominal incision.

In two instances in this series, there was associated adnexal disease while in the untreated group, adnexal disease was present on six occasions.

Referring to Table I, it will be seen that considering any or all criteria, no demonstrable effects are observed from the local use of sulfonamides.

TABLE I

COMPLETE HYSTEREC- TOMY	AVERAGE NUM- BER OF FEBRILE DAYS (AFTER 72 HRS.)	FEVER OVER 101°	WOUND INFECTION	COMPLI- CATIONS	DAY OF DIS- CHARGE (AVER- AGE)	DEATHS
Without sulfanil- amide 13 cases	3	9 or 69%	0 or 0%	Vaginal hemorrhage on 15th day 1 or 7%	15	0
With sulfanil- amide 13 cases	6.5	10 or 77%	2 or 15%	1. Parame- tritis 2. Parame- tritis and fecal fistula 2 or 15%	19.8	0

B. Adnexal Disease Without Known Peritoneal Contamination

In 14 cases, sulfonamide drugs were placed in the abdominal cavity because of the presence of adnexal disease manifesting a greater or lesser degree of acute or subacute inflammatory reaction. The induration of the tissues and structures not removed plus the existence of raw surfaces and shreds of inflammatory exudate seemed to suggest that local sulfonamide action might prevent bacterial growth in these favorable media and, therefore, prevent postoperative complications due to infection. Usually about 5 Gm. of powdered drug were placed about the operative site and in the lower abdominal cavity. In all but 5 cases, an additional 2 Gm. were placed in the layers of the abdominal incision during closure.

In the untreated group, while the cases are grossly comparable, it must be stated that in general the degree of inflammatory reaction was somewhat less marked. As would be inferred, the drug was principally used in the cases showing the greater evidence of active infection.

In any event, the comparative results listed in Table II, would not seem to indicate that the use of the drug had brought about any striking improvement in the postoperative courses of the 14 patients reported.

C. Adnexal Disease With Gross Operative Peritoneal Contamination

In 14 cases, the spill of frankly purulent or probably infected material into the peritoneal cavity during operative manipulation constituted the indication for local use of sulfonamides. On all occasions, the source of spill was either a pyosalpinx or a tuboovarian abscess.

TABLE II

ADNEXAL DISEASE WITHOUT CONTAMINATION OF PERITONEAL CAVITY	AVERAGE NUMBER OF FEBRILE DAYS (AFTER 72 HRS.)	FEVER OVER 101°	WOUND INFECTION	COMPLICATIONS	DAY OF DISCHARGE (AVERAGE)	DEATHS
Without sulfanilamide 14 cases	1.9	10 or 70%	2 or 14%	Intestinal obstruction 1 or 7%	16	0
With sulfanilamide 14 cases	2.7	7 or 50%	1 or 7%	Thrombophlebitis 1 or 7%	20	0

The cases chosen for comparison with this group are essentially identical, the source and type of infected material being the same.

Approximately the same use was made of the drugs in these cases as was described in the previous group, although in a few instances as much as 10 Gm. total were employed. In only 5 cases, however, was additional drug reported placed in the layers of the incision.

As in the previous groups, examination of the comparative results with and without drug in Table III, reveals no evidence to support a conclusion that the drugs exerted any valuable effect.

TABLE III

ADNEXAL DISEASE WITH GROSS CONTAMINATION OF PERITONEUM	AVERAGE NUMBER OF FEBRILE DAYS AFTER 72 HRS.	FEVER OVER 101°	WOUND INFECTION	COMPLICATIONS	DAY OF DISCHARGE (AVERAGE)	DEATHS
Without sulfanilamide 14 cases	1.7	10 or 71%	0 or 0%	Parametritis 1 or 7%	14.5	0
With sulfanilamide 14 cases	4.9	11 or 78%	1 or 7%	1. Parametritis 2. Parametritis 3. Pulm. embolus 3 or 21%	18.3	0

D. Preoperative Pelvic or Generalized Peritonitis

Only 5 cases of pelvic or generalized peritonitis were subjected to surgery on the gynecologic service during the period of study. All of these patients were acutely ill at the time of operation and 4 of them were known to have large pelvic inflammatory adnexal masses, unsuccessfully treated by conservative measures. In the fifth case, peritonitis was the result of a vigorous vaginal douche with concentrated magnesium sulphate used in an effort to induce abortion, and probably was not primarily infectious in origin. Of the 4 adnexal disease cases, the 3 that recovered were operated on fairly promptly while the patient who died refused operation until approximately 16 hours after a large tuboovarian abscess was believed to have ruptured. All of these patients were drained either abdominally or vaginally and the amount of drug deposited in the abdominal cavity varied between 10 and 15 Gm. The results are listed in Table IV.

TABLE IV

PREOPERATIVE PERITONITIS	AVERAGE NUMBER OF FEBRILE DAYS AFTER 72 HRS.	FEVER OVER 101°	WOUND INFECTION	COMPLICATIONS	DAY OF DISCHARGE (AVERAGE)	DEATHS
With sulfanilamide 5 cases	8	3	0	0	25	1

Unfortunately, no suitable cases were found in which sulfonamides were not used to compare with this group. However, it might be concluded justifiably that the recovery of 4 out of 5 patients gravely ill from this very serious disease would indicate the liberal use of sulfonamides locally in all cases of peritonitis as a routine measure, since in the past the mortality rate from this complication has always been extremely high.

Discussion

On evaluating the results of the local use of sulfonamide drugs in gynecologic operations performed on the types of cases analyzed, it is rather surprising even in so small a series that, with the exception of Group D, no particular value could be ascribed to their use. No significant toxic reactions were noted, sulfanilamide being employed in thirty-nine cases and sulfathiazole in the remaining seven. In most instances, however, the total amount of drug used did not exceed 8 Gm., a dosage which might be considered too small. This possibility is enhanced by the finding of Lockwood that when the concentration of sulfonamide inhibitors is high, the concentration of the drug must be correspondingly high. Certainly in the presence of long-standing adnexal disease with resulting productive inflammatory reaction, loculated pus and peritoneal exudate, one might anticipate substantial concentrations of inhibitors. Again, a second of Lockwood's principles is not effective here, since the local cellular defenses of the pelvic peritoneum cannot be considered very active in cases of chronic salpingitis of long duration. In the recovered cases of peritonitis, it is plausible to assume that the favorable results were due more to the protection of the freshly contaminated extrapelvic peritoneum than to local effect on the original focus.

While cultural studies were not made in all cases, in most instances in which cultures were reported, organisms of low virulence were recovered. Similarly, in complete hysterectomy, where contamination of the peritoneum results from opening the vaginal vault, bacteria of marked pathogenicity would not be encountered commonly.

These several considerations may be of significance in explaining the failure of sulfonamide drugs to produce the dramatic results in the cases reported here which have rather consistently been noted in other branches of surgery. In the only article found in the literature discussing the value of local sulfonamides in obstetric and gynecologic operations (Bibb—1942),² the results in similar cases were rather uncon-

vineing although the conclusion was drawn that a step in the right direction had been taken.

Summary and Conclusions

1. A brief review of Lockwood's principles relative to the use of sulfonamide drugs as an aid to surgery is presented.

2. An analysis is made of 46 cases in which sulfonamide drugs were used locally in gynecologic operations in comparison with an essentially similar group of cases in which sulfonamide drugs were not used. (Group D excepted.)

3. Excluding Group D (peritonitis), this analysis and comparison demonstrated no effects, either favorable or unfavorable, which could be attributed to the use of these drugs locally in the abdominal cavity.

4. Pathologic factors peculiar to the types of gynecologic cases presented are offered as possible explanations for the apparent lack of value of local sulfonamide therapy in these cases.

5. Four of five patients suffering from peritonitis of pelvic origin recovered, sulfonamide drugs being used locally at operation. This is thought to be suggestive, though not conclusive, evidence that therapy was effective.

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THE LACTOGENIC EFFECT OF PROLACTIN IN THE HUMAN BEING*

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GROWTH and secretion of the mammary glands are controlled mainly by hormones, but different hormones are involved in these two distinct processes. The anterior lobe of the pituitary exercises a direct control over milk secretion through its lactogenic principle, prolactin, and over the development and growth of the mammary glands through a mammogenic hormone. In addition, the anterior hypophysis exerts an indirect control of the structure and function of the breasts through the medium of the ovarian sterols, estrogen and progesterone.

Both mammary growth and lactation were observed, as early as 1928, to follow the administration of crude pituitary extracts in vaginal experimental animals with intact ovaries by Stricker and Grueter¹ and others. The enlargement of the crop sac of pigeons with the formation of "crop milk" was reported in 1931 by Riddle and Braucher.² All of these earlier results were obtained with simple pituitary extracts but did not demonstrate the identity of the specific hormone involved.

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The isolation of the hypophyseal hormone that excites lactation was established in 1932 to 1933 by Riddle, Bates and Dykshorn³ who called it prolactin. Confirmation of the hormone's individuality and lactogenic function was shortly thereafter supplied by Catchpole and Lyons,⁴ by Gardner and Turner⁵ and others. In 1935, Bates and Riddle⁶ described an improved method of extraction and a more accurate standardization of the substance by assaying its stimulating influence on the growth of the crop gland of pigeons.

Lactogenesis involves preparation of the breast by estrogen and progesterone. Prolactin then initiates and maintains milk secretion. Prolactin is formed by the eosinophilic cells of the anterior lobe of the pituitary.⁷ As isolated in crystalline form, prolactin is stable, water soluble and has a pH 3 to 4. It has not yet been chemically identified but it seems to be free from antigenic proteins.

In the experimental animal, prolactin controls carbohydrate metabolism, augments growth, inhibits estrus, elevates the basal metabolism rate and evokes maternal behavior. Prolactin, as well as the earlier crude pituitary extracts, often increases the milk yield of domestic animals, although the reports concerning this effect are by no means uniform.

In the earliest clinical trials of prolactin, Kurzrok⁸ improved the lactation in twenty-five of twenty-nine women by the administration of from 75 to 400 I. U.* between the sixth and ninth post-partum days. Evans⁹ later reported successful trials with total doses of from 1,000 to 2,500 I. U. Ross¹⁰ used larger doses, such as 400 to 1,000 I. U. twice daily on the sixth and seventh days post partum, to increase milk secretion. Employing similar doses, Stewart and Pratt¹¹ obtained no significant increase in milk secretion. Kenny and King¹² caused lactation to become sufficient in 74 per cent of treated women as compared to a sufficient supply of milk in 19 per cent of untreated women. Weiner¹³ failed to produce lactation in castrated girls by the combined use of estrogenic hormones and prolactin. In our experience, prolactin is a fairly effective means of initiating and increasing milk secretion in puerperal women.

In our work with prolactin (Schering), three groups of puerperal patients were studied as follows:

Experiment 1.—In the first group of forty puerperal women, twenty were given prolactin and twenty were used as controls. The forty comprising the two groups, treated and untreated, were not permitted to nurse their infants because of prematurity, etc. Prolactin injections of 100 I. U. twice daily were started on the first post-partum day and continued for five consecutive days. Pumping of the breasts of all the patients every eight hours was begun the day after prolactin was started and continued for five days. In all patients, the amount of milk per pumping and the output per day were noted. Results show that the average quantity of milk secreted by the prolactin-treated mothers was more than twice the average quantity secreted by the untreated women (Table I). The smallest quantity of milk obtained

*One international unit is the specific activity contained in 0.1 milligram of the standard preparations established by the Health Organization of the League of Nations.

per day from mothers receiving prolactin was 12 ounces on the fifth day; the largest quantity $25\frac{1}{2}$ ounces. In the control group, the lowest output on the fifth day was 3 ounces; the highest was no more than $13\frac{1}{2}$ ounces.

TABLE I. LACTOGENIC EFFECT OF PROLACTIN IN POST-PARTUM WOMEN AS MEASURED BY THE AVERAGE DAILY MILK YIELD OBTAINED BY PUMPING

DAY OF PUMPING	PROLACTIN TREATED GROUP OF 20	CONTROL GROUP OF 20
	AVERAGE DAILY QUANTITY MILK PER PATIENT	AVERAGE DAILY QUANTITY MILK PER PATIENT
1	oz. $1\frac{1}{2}$	oz. 0
2	oz. 3	oz. $\frac{3}{4}$
3	oz. $7\frac{1}{2}$	oz. 3
4	oz. $13\frac{1}{2}$	oz. 6
5	oz. $19\frac{1}{2}$	oz. $10\frac{1}{2}$

Experiment 2.—One hundred patients were given 100 I. U. of prolactin twice daily from the first to the fifth day post partum, inclusive. One hundred similar patients were used as controls. Both the control and treated patients were equally divided as to ward and private status. The infants of the treated and control groups were breast-fed during the ten days of observation. The infants were nursed at intervals of four hours beginning twelve hours after birth. The infants whose mothers received prolactin lost less weight and regained weight faster than the infants of the control group. Three-fourths of the infants regained or exceeded their birth weight within the ten-day period when prolactin was used, whereas only one-sixth of the control group regained their birth weight during that period (Table II).

TABLE II. EFFECT ON INFANTS OF 100 UNITS OF PROLACTIN ADMINISTERED TO MOTHERS TWICE DAILY FROM THE FIRST TO THE FIFTH DAY, POST PARTUM

	NUMBER OF INFANTS OF 100 TREATED MOTHERS	NUMBER OF INFANTS OF 100 CONTROL MOTHERS
Average number of days from birth until infant showed gain in weight	2.3	3.1
Percentage of body weight loss	4.3%	5.7%
Infants regaining birth weight within ten days	83%	37%

The type of delivery, spontaneous or operative, the parity of the mother and the sex of the child had but little bearing on the results of this study. Infants who were injured during birth were not used in this study.

Only twenty-five of each group were followed up for three months. Twenty of the infants whose mothers received prolactin were still breast-fed. Breast feeding of the remaining five was discontinued because of inconvenience or fissured nipples. Twenty-three of the twenty-five in the control group, followed up for three months, were still nursing their infants.

Experiment 3.—Prolactin, 100 I. U. twice daily for five days, was given to improve the yield of milk in a group of fifty lactating women when it was apparent, from five to seven days after birth, that the milk supply was markedly insufficient as determined by the excessive weight loss of the infants maintained solely by breast feeding.

The results obtained were as follows: Thirty-six of the fifty patients (72 per cent) showed a definitely good response. Of the remaining

fourteen patients, four (8 per cent) exhibited partial improvement and ten (20 per cent) showed no response.

The reactions to injections of prolactin, observed in our 170 patients, may be classified as local and systemic. Locally pain at the site of injection was the most common complaint. Redness and swelling were noted in about 10 per cent of the women who complained of pain. There was not a single case of suppuration at the site of injection. Moderate elevation of temperature occurred in only three patients. It was ascribed to prolactin after all other factors were eliminated. The temperature receded to a normal level within 24 hours after withdrawal of the prolactin. Engorgement of the breasts without elevation of the temperature was present in twelve patients. Although it was also relieved by discontinuing the prolactin, a free flow of milk remained.

Summary

1. The effect of prolactin on the secretion of milk in one hundred and seventy puerperal women divided in three groups was studied.

2. In the first group of twenty women whose infants could not be put to the breasts for various reasons, pumping of the breasts at regular intervals yielded more than double the quantity of milk than in the control group.

3. In the second group of one hundred private and ward patients, 85 per cent of the infants regained their birth weight ten days after delivery. Only 30 per cent of the control group regained their birth weight without the aid of bottle feeding.

4. The type of delivery, spontaneous or operative, parity of the mother and sex of the child had but little influence on the results.

5. In the third series of fifty women, prolactin was used to improve lactation when it was apparent by the rapid loss of weight of the infants that the milk supply was insufficient to maintain the life of the infants. A good response was obtained in 72 per cent of the fifty women; partial response in 8 per cent and no response in 20 per cent.

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SEVERE PRE-ECLAMPSIA*

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ALTHOUGH much has been written about the toxemias of pregnancy there is still no well accepted cause nor completely satisfactory type of treatment for severe pre-eclampsia or eclampsia. However, a careful study of all such cases might ultimately lead to a clearer understanding of this complication of pregnancy. We define severe pre-eclampsia as that type of toxemia occurring most frequently in the third trimester of pregnancy showing two or more of the following symptoms or signs: (1) a sudden sharp rise of blood pressure; (2) moderate to large amounts of albumin in the urine; (3) elevation of uric acid and lowering of CO_2 combining power in the blood; (4) varying degrees of edema and accompanied by (5) such symptoms as headache, epigastric pain, visual disturbance and (6) rapid gain in weight. In this clinic, severe pre-eclampsia and eclampsia are considered to be the same disease entity. Severe pre-eclampsia if not effectively treated may result in the more severe form of the disease and terminate in convulsions. The disease is then classified as eclampsia.

From September 1, 1932, until December 31, 1942, there were, in the Woman's Clinic of the New York Hospital, 332 cases of severe pre-eclampsia, 42 of whom developed convulsions after admission to the hospital and after varying periods of treatment. These 42 cases, therefore, represent failures in our treatment of severe pre-eclampsia. Twenty additional cases of eclampsia occurring during the above period have not been included because they had a convulsion prior to admission to the hospital, and had not been under observation in this clinic during the antenatal period.

Incidence

These 332 cases of severe pre-eclampsia and eclampsia occurred in a total of 37,937 pregnancies, giving an incidence of 0.87 per cent. The incidence for severe pre-eclampsia alone is 0.76 per cent. Our clinic incidence for all toxemias is 7.12 per cent, and severe pre-eclampsia and severe pre-eclampsia followed by convulsions represent 12.2 per cent of all the toxemias.

The distribution of cases between the white and black races was 91.03 per cent to 8.97 per cent, respectively. In our clinic 8.3 per cent of the patients are black, so the disease apparently is not more common in one race than in the other. Of the 332 severe pre-eclampsia and eclampsia cases 44, or 13.25 per cent, occurred in private patients. The incidence of private deliveries in our clinic is 17.7 per cent, so that the

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incidence of the disease is appreciably less in private patients than in ward patients.

Of the 290 patients with severe pre-eclampsia, 193 or 66.6 per cent were in their first pregnancy, 50 or 17 per cent in their second, and 47 or 16.4 per cent in their third or more; the highest parity was in one patient having her tenth pregnancy. In the clinic as a whole there have been 48.3 per cent of primigravidas and 51.7 per cent of multigravidas. In the eclamptic group 36 or 85 per cent were in their first pregnancy, 1 or 4 per cent was in a second pregnancy, and 5 or 11 per cent had had two or more pregnancies. Severe pre-eclampsia, and to a greater extent severe pre-eclampsia followed by convulsions is definitely a disease of patients pregnant for the first time.

Only 35 of these two groups of cases gave a history of previous diseases that might have a bearing on their condition. These are so few and so scattered as to be of no significance. Scarlet fever, the commonest, occurred in only 21 of the group. Twenty-two of the severe pre-eclampsies and 2 of the eclampsies gave a history of a previous toxemia, and 24 of the severe pre-eclampsies and one of the eclampsies had a toxemia in a subsequent pregnancy. Three patients, only, had severe pre-eclampsia twice in our clinic. None of the patients with eclampsia had a subsequent eclampsia or severe pre-eclampsia.

TABLE I. SYMPTOMS AND SIGNS OF SEVERE PRE-ECLAMPSIA

1. Sudden Sharp Rise in Blood Pressure.
2. Moderate to Large Amounts of Albumin in the Urine.
3. Elevation of Uric Acid and Lowering of CO_2 in the Blood.
4. Varying Degrees of Edema.
5. Headache, Epigastric Pain, Visual Disturbances.
6. Rapid Gain in Weight.

Table II shows the age incidence expressed in percentage for various five-year periods. It can be seen that 60.3 per cent of severe pre-eclampsia occurred between the ages of 25 and 34. Comparing this with the age group for the clinic as a whole, it is seen that 57.9 per cent of our obstetrical patients are between the ages of 25 and 34. The greatest number of patients with eclampsia (35.77 per cent) are delivered between the ages of 20 and 24.

TABLE II. AGE INCIDENCE IN PER CENT

	AGE -20	20 TO 24	25 TO 29	30 TO 34	35 TO 39	40+
Clinic (1936)	3.5	27.5	34.6	23.3	9.6	1.8
Severe Pre-eclampsia	3.7	22.4	31.7	28.6	10.0	3.4
Eclampsia	9.5	35.7	16.6	23.9	9.5	4.7

Of the 290 cases of severe pre-eclampsia, 11 or 3.7 per cent occurred before the twenty-seventh week, or in the second trimester of pregnancy. One hundred cases, or 34.4 per cent, occurred before the thirty-fifth week, or probably at a time when the chances of getting a viable infant were poor. There seems to be very little relationship between the period of gestation and the weight of the baby in this disease. We arbitrarily studied all babies born in the thirty-seventh week of gestation and found that these 24 babies varied in weight from 1,140 grams to 4,565 grams. Six of these babies weighed under 2,000 grams, and 11 of them under 2,500 grams. Only three of the babies were born dead, and of these only one was macerated, so there cannot have been

any post-mortem loss of weight to account for the small size of the fetus.

In the eclamptic group only one case occurred in the second trimester, and 14 or 33.3 per cent occurred before the thirty-fifth week. There were only three babies born in the thirty-seventh week, weighing 1,960, 2,000 and 2,350 grams, respectively; one was stillborn.

The average weight gain for the severe pre-eclampsia group was 26.8 pounds and for the eclampsia group, 27.3 pounds. Since this is about the same gain as that considered normal during pregnancy by most clinics, it must be added that our weight gain for each patient was that noted at the time of admission. We compared the weight gain of our patients in weekly groups from the thirty-fourth week to term with those of normal pregnancies, but because of the small number in each week in our series no conclusions could be drawn.

Several other observations have come out of this study. There were 10 sets of twins (8 in severe pre-eclampsics, 2 in eclampsics), an incidence of 3.07 as compared with the clinic incidence of 1.03 per cent. There were 27 breech presentations (21 in severe pre-eclampsics and 6 in eclampsics), an incidence of 8.1 per cent as compared with that of the clinic of 4.13 per cent. There were eight cases of ante-partum bleeding in the patients with severe pre-eclampsia, 4 or 1.3 per cent of which were due to premature separation, and 3 or 1 per cent were due to placenta previa. The clinic incidence for premature separation is 0.396 per cent and for placenta previa, 0.552 per cent, so that the percentage figure in our series for premature separation is three times as high as the clinic incidence, and for placenta previa twice as high. One patient in the severe pre-eclamptic group had the disease with a blood pressure never above 140/90, while the highest elevation was 270/140, and the average was 179/113. The lowest elevation in the eclamptic group was 160/100 and the highest 270/170 with an average elevation of 194/118. The CO₂ combining power in the severe pre-eclampsics averaged 41.61, ranging from 21.7 to 55.6, and in the eclampsics the average was 38.02, with the range from 23 to 41.5. The uric acid averaged in the former 4.88, and in the latter 5.55.

Treatment

Tables III and IV show the various types of treatment employed, some patients having more than one type. The treatment of these cases fell into two categories on admission. If the pre-eclampsia was

TABLE III. MEDICAL TREATMENT

	SEVERE PRE-ECLAMPSIA	ECLAMPSIA
Modified Stroganoff	64	14
Routine glucose, rest in bed, sedatives, low salt diet	142	15

TABLE IV. ONSET OF LABOR AND TREATMENT

	SEVERE PRE-ECLAMPSIA	ECLAMPSIA
Spontaneous	167	22
Induction by:		
Bag	25	5
Bougie	8	6
Artificial Rupture of Membranes	6	0
Medical	106	11

not too fulminating, routine treatment was given. This consists of rest in bed, sedatives if indicated, plus a low protein, low salt diet. This was used in 142 severe pre-eclampsies and 15 eclampsies. Otherwise, a modified Stroganoff regime was started. This consisted of morphine sulfate, two $\frac{1}{4}$ grain doses, and chloral hydrate, 4 doses. This was given at stated intervals and tried in 64 pre-eclampsies and 14 eclampsies. Intravenous glucose was given if thought necessary in conjunction with both of the above methods. Molar lactate was given when the CO_2 fell below 35 volumes per cent. Intramuscular injection of magnesium sulfate was never used. If, despite the above types of treatment, the patient became worse and failed to go into spontaneous labor, induction or cesarean section was usually done. It has long been felt that a toxemia leads to an increased irritability of the uterus. (Table IV.) The fact that 167 of the severe pre-eclamptic group and 22 of the eclamptic, or 56.9 per cent, went into labor spontaneously would seem to add further proof to this feeling until we consider that 93.6 per cent of our clinic patients have a spontaneous onset of labor. In many of these cases labor started from one to several days after a medical induction had failed. Medical induction was tried 142 times in 106 patients with severe pre-eclampsia, failing 96 times. In 15 cases of eclampsia it was tried 12 times, failing in only three instances. To induce labor by surgical means the Voorhees bag was used in 25 severe pre-eclampsies and 5 eclampsies, the bougie in 8 of the former and 6 of the latter. The bougie has been used only twice since 1935. Artificial rupture of the membranes was the method of induction in 6 cases of severe pre-eclampsia and in none of the eclampsies.

It is our feeling from studying these cases that a typical severe pre-eclampsia does not improve appreciably under either of the medical forms of treatment. If the blood pressure is taken at two-hour intervals there are times during the course of the day when it may be at lower levels for two or three readings, but it inevitably returns to dangerous levels. In our group of 332 cases only 52 showed any definite improvement before delivery, or before the first convulsion. One hundred and fifty-four of the 280 cases who failed to show improvement went into labor spontaneously while under treatment, leaving 126 cases who did not improve and who, therefore, needed to be induced or delivered. It is very difficult to separate the milder forms of severe pre-eclampsia from mild pre-eclampsia, and we feel that some of our cases that showed improvement might well be in this border line group. We were impressed by the obvious lack of improvement in the real fulminating cases.

Table V shows the method of delivery used in this series of cases. One hundred and sixty-four of the cases of severe pre-eclampsia delivered spontaneously and 124 had operative deliveries. Of the 124 operative cases, 68 of the operations were done because of the pre-eclampsia. A total of 27 cesarean sections in the severe pre-eclampsia group was done, 21 for the disease and 6 for other indications such as premature separation, contracted pelvis, and so forth.

TABLE V. TYPE OF DELIVERY

	SEVERE PRE-ECLAMPSIA	ECLAMPSIA
Abortions, spontaneous	2	0
Spontaneous	164	13
Operative	124 { Vaginal 97 Abdominal 27	29 { Vaginal 26 Abdominal 3

In the 21 sections done for the disease two were miniature sections. In the remaining 19 cases only two of the babies failed to survive; one delivered in the thirty-third week weighed 1,390 Gm. and lived 23 days before dying due to prematurity; the other delivered in the thirty-seventh week, weighed 1,260 Gm. and died at the end of five weeks of a septicemia originating in the cord. Two infant deaths in the 19 cases give a fetal mortality of 10.5 per cent as compared to that of 20 per cent for the whole series. The incidence of sections in the 290 cases is 9.3 per cent.

In the eclampsia group there were 29 operative deliveries in the 42 cases. The disease itself was the indication for operation in all but 3 of the 29. To list the three exceptions: one low forceps was done for severe pre-eclampsia and the patient had a convulsion soon afterward; another low forceps was done for prolonged second stage; and a classical cesarean section was done for renal disease, the eclamptic convulsion occurring eighteen hours after delivery. All three babies delivered by cesarean section lived.

Results

There were no maternal deaths in the 290 cases of severe pre-eclampsia and one death in the 42 cases of eclampsia. This gives a maternal mortality of .30 per cent for the 332 cases. A short summary of the history of the patient who died follows.

The patient was a 21-year-old white primigravida with a negative past history whose E.D.C. was September 2, 1937. She was followed in our out-patient clinic at regular intervals from March 25, 1937, until admission to the hospital on October 6, 1937. The blood pressure on September 2nd, was 90/60, but one week later showed a sudden rise to 144/90. During the next four weeks the systolic pressure varied from 120 to 140 and the diastolic between 80 and 90. There was a 2-plus albumin on September 29, and 4-plus on the day of admission. The weight gain was 30 kg. total, with a gain of 17 kg. in the last trimester. There were no subjective symptoms at the time of admission: uric acid was 4.2; CO_2 , 42.4; albumin, $1\frac{1}{2}$ Gm. per liter; blood pressure 150 to 155/100 on October 7th, and 8th. Labor began spontaneously at 4:00 P.M. on the 8th of October, pains were very good by midnight, but the pressure was 190/115 and the patient complained of severe headache. Morphine, $\frac{1}{4}$ grain, was given at 12:45 A.M. on the 9th. The first convulsion occurred at 1:30 A.M. on the 9th, fifty-five and a half hours after admission. She had twelve convulsions before delivery. Labor lasted 32 hours; she was delivered while in deep coma without an anesthesia. The baby survived. She had two more convulsions post partum and died ten and a half hours after delivery. Treatment consisted of Stroganoff plus atropin, digitan, intravenous glucose and nasal oxygen, but she never responded to any treatment. Autopsy showed peripheral necrosis and thrombosis in the liver and bronchopneumonia. It might be that had this patient, because of her excessive weight gain and elevation of pressure near term, been admitted sooner this catastrophe could have been avoided. She delivered more than five weeks past her expected date of confinement and certainly had a fulminating type of toxemia once labor started.

Table VI shows the gross fetal mortality in the pre-eclampsia group and lists those cases in which a definite cause of death was noted. These have been arranged according to the weight of the fetus and the

TABLE VI. INFANTILE MORTALITY IN SEVERE PRE-ECLAMPSIA

WEIGHT IN GRAMS	GESTATION IN WEEKS	TOTAL DEAD	STATED CAUSE OF DEATH
-1,000	20-30	8	
1,000 to 1,499	29-39	16	Malformation . 1 Infected Cord 1 Pneumonia 1
1,500 to 1,999	29-38	7	
2,000 to 2,499	35-44	8	
2,500 to 2,999	36-42	7	Malformation 1 Premature Separation 1
3,000 to 3,499	36-45	7	Intracranial Hemorrhage 3 Erythroblastosis 1
3,500+	27-43	4	Intracranial Hemorrhage 1
Unknown	41	1	
TOTAL		58	10
Incidence of mortality, 19.46%			

duration of pregnancy in weeks. In the severe pre-eclampsia group 58 babies, or 19.46 per cent, were lost; 48 of these are presumed to have succumbed because of the disease. Table VII shows 13, or 29.54 per cent, were lost in the eclamptic group, 10 of whom apparently died because of the eclampsia. It can be seen from the table that the weight of the baby varies considerably in the same period of pregnancy. There were 31 dead babies in the severe pre-eclampsia group who weighed under 2,000 Gm., and 21 that survived. In the eclamptics five under 2,000 Gm. died and one lived. This means that 62.07 per cent of the babies under 2,000 Gm. died. In the clinic as a whole only 37.98 per cent of these babies die.

TABLE VII. INFANTILE MORTALITY IN ECLAMPSIA

WEIGHT IN GRAMS	GESTATION IN WEEKS	TOTAL DEAD	STATED CAUSE OF DEATH
-1,000	32	1	
1,000 to 1,499	27-33	3	
1,500 to 1,999	38	1	
2,000 to 2,499	33-38	3	Premature Separation . 1
2,500 to 2,999	33-39	2	Erythroblastosis 1
3,000 to 3,499	41-42	2	
3,500+	39	1	Intracranial Hemorrhage 1
TOTAL		13	3
Incidence of mortality, 29.54%			

Ninety-nine patients admitted prior to the thirty-fifth week of pregnancy were continued on conservative treatment despite lack of improvement until the baby was thought to be viable. Of this group 61 delivered babies that survived and 38 had babies either stillborn or who died in the neonatal period.

Follow-Up

Two hundred and thirty-one of the severe pre-eclampsias were seen in the clinic at six weeks' post partum. Of this number 74 had elevations in blood pressure (140/90 or above) and 157 were normal, as shown in Table VIII. In the follow-up of from one to nine years 43 patients, or 14.82 per cent of the whole group, had elevations of blood pressure. If we count only the patients followed, eliminating those who did not return post partum, we have 17.26 per cent with an ele-

TABLE VIII. FOLLOW-UP

	SEVERE PRE-ECLAMPSIA BLOOD PRESSURE		ECLAMPSIA BLOOD PRESSURE	
	6 WEEKS	ELEVATED 1 TO 9 YEARS	6 WEEKS	ELEVATED 1 TO 9 YEARS
Normal	157	9	23	0
Elevated (140/90 or above)	74	32	6	2
Did not return	59	2	12	1
Died			1	
TOTAL	290	43	42	3

vation of blood pressure. The histories of the 43 who had elevations were investigated further and only nine of these gave a history of a previous toxemia; three gave a history of scarlet fever, and one had a kidney infection. Since two of these complications occurred in the same patient, we have 12 patients who might have suffered previous kidney damage. This leaves 31 out of 290, or 10.7 per cent, who suffered permanent kidney damage as a result of this severe pre-eclampsia.

The eclamptic patients returned so poorly even to the six weeks post-partum clinic that the figures do not warrant any comment.

Seventy-one of the 290 patients had a subsequent pregnancy in our clinic. Of this group 47 were considered normal in their subsequent pregnancy and 24 had another toxemia—the types are listed in Table IX. The follow-up in the eclamptic group again was inadequate.

TABLE IX. STUDY OF SUBSEQUENT PREGNANCIES

	SEVERE PRE-ECLAMPSIA	ECLAMPSIA
No Toxemia	47	1
Toxemia—Severe Pre-eclampsia	2	0
Eclampsia	1	0
Mild Pre-eclampsia	6	1
Hypertensive Disease	4	0
Renal Disease	3	0
Unclassified	8	0
	71	2

Discussion

We feel from this study that the treatment of severe pre-eclampsia as outlined gives excellent results as far as the mother is concerned. One maternal death in 332 cases is a very low figure. Of interest is the fact that there were no additional maternal deaths in the 20 cases of eclampsia not included in this study. The fulminating cases of severe pre-eclampsia do not improve under conservative treatment, responding apparently only to termination of the pregnancy. It might be possible to deliver this group earlier and perhaps improve our fetal mortality figures.

With this in mind, we have studied very carefully the 58 cases of severe pre-eclampsia in which the babies died. Seventeen of these patients showed temporary improvement for two to six hours within the first forty-eight hours after admission. Of these 17 babies, nine weighed 2,000 Gm. or over, and all died after the period of improvement and before any attempt was made to get the patient into labor

or deliver her. This period of improvement was so short as to be of little value, but we would like to make the point that had labor been induced or delivery effected earlier in the hospital stay, a living baby might have been obtained. In the eclamptic group eight out of 13 dead babies fell into this same classification.

In patients who do not improve continuation of the conservative method of treatment with the hope of carrying a baby to viability is of questionable value, because the weight of a baby at a given period in pregnancy in this disease seems to be subject to extreme variation. The great advantage in continuing the conservative treatment in the absence of improvement is that 46.3 per cent of our patients went into labor spontaneously, thus relieving us of any decision concerning intervention.

Another group of patients seems to develop the severe pre-eclampsia after a period of observation in the outpatient clinic during which they had slight elevations of blood pressure and would be classed as mild pre-eclampsia. How to separate this group from those who have only mild pre-eclampsia, without admitting every patient who has a rise in blood pressure, it is difficult to say. Many of our series seemed to have a fluctuating blood pressure for several weeks before the severe symptoms developed; that is, although the pressure returned to normal for a week following an elevation, it promptly rose again.

We feel that if all these patients with elevations in blood pressure could be admitted and carefully studied, and consideration of delivery given in those who did not respond to treatment, more living babies might be obtained and the 17.26 per cent who had elevations of blood pressure after long follow-up periods might be decreased.

Practically every case in our series who had been admitted for toxemia and discharged improved and undelivered came back very soon and usually in poor condition. We think that great consideration should be given before any toxemia patient is discharged undelivered.

The number of patients, 17.26 per cent, who had an elevation of blood pressure after one year or more of follow-up is high and makes us feel that severe pre-eclampsia results in as much permanent kidney damage as eclampsia. Even when we eliminate from this group all patients who might have suffered kidney damage prior to the severe pre-eclampsia we see that one patient in every ten has signs of permanent renal damage.

Conclusions

1. Severe pre-eclampsia and severe pre-eclampsia followed by convulsions occurred in 0.87 per cent of the pregnancies delivered in this clinic and represent 12.2 per cent of all the toxemias complicating pregnancies.

2. The weight of the infants apparently has very little relationship to the expected date of confinement.

3. There was one maternal death due to eclampsia in this group of 332 cases studied, giving an incidence of three per thousand patients.

4. The gross infantile mortality rate is 20.7 per cent as compared to 3.4 per cent in the clinic as a whole. Of 71 infant deaths 58, or 81.6 per cent, died from prematurity or the disease.

5. In the follow-up of the severe pre-eclamptic group 32.1 per cent of the patients had an elevated blood pressure when seen six weeks post partum and 17.3 per cent when followed from one to nine years.

6. Of 332 cases 52 showed definite improvement; 154 of the remaining 280 went into labor spontaneously after a period of treatment. This leaves only 126 who did not improve and had to be delivered or have labor induced.

7. In those patients who do not respond to the conservative treatment earlier delivery might decrease the fetal mortality.

8. Immediate hospitalization for severe pre-eclampsia is advised, and discharge before delivery, even if the patient seems improved, is to be discouraged.

9. Ten sets of twins occurred in our 332 cases, giving an incidence of 3.07 per cent which is three times the clinic incidence.

20 EAST SEVENTY-SIXTH STREET

HEMATOMA OF THE RECTUS ABDOMINIS MUSCLE IN PREGNANCY

Report of Case and Review of Literature

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A STUDY of the diseases of the rectus abdominis muscle should begin with the classic monograph on the anatomy of this structure by Max Brodel.¹ He showed that the muscle, divided at intervals by ligamentous septa into four muscle bellies, is quite completely covered by a strong tendinous sheath at all parts except the lower posterior aspect where the muscle fibers are in close approximation to the peritoneum.

Between the muscle and the peritoneum in this region, runs the large inferior epigastric artery with its branches which penetrate the two lower muscle bellies, and it anastomoses with the descending branches of the superior epigastric artery, whose branches penetrate the two upper muscle bellies. A hematoma in the lower half of the muscle is more apt to cause peritoneal irritation because of the absence of the posterior sheath.

In the literature the etiologic factors in the rather rare condition of spontaneous hematoma of the rectus muscle are shown to be:

(a) Trauma, as in recently recruited soldiers, and in athletes, and in strain of labor, or coughing in pregnancy.

TABLE

AUTHOR	YEAR REPORTED	RACE	AGE	GRAVIDA	MONTH OF PREGNANCY	PREGNANCY
1. Stoeckel	1901	W	Not stated	4	6	Aborted.
2. Stoeckel	1901	W	Not stated	6	Term	Spontaneous delivery.
3. Sjoblom	1906	W			9	
4. Vogt	1913	W	21	3	Term.	Spontaneous delivery.
5. E. Toft (Cullen)	1915	W			6	
6. Andrews (Cullen)	1916	W	39		8	Spontaneous labor
7. Lichtenstein	1920	W	32	1	10	Spontaneous delivery.
8. Decio (Carretti)	1922	W	16	Multipara	6	
9. Farrel	1923	W		Multipara	Term	Cesarean section.
10. Carnelli	1929	W	30	5	5	Aborted 5 days postoperatively.
11. Schroeder	1929	W	32	3	Term	Terminated by cesarean section.
12. Abelin	1930	W	40	6	?	Stillborn twins at 7 mo. Cesarean section.
13. Lantuejoul et al.	1933	W	26	3	7	Stillbirth.
14. Brindeau	1934	W	36	Multipara	5	Continued to term. Spontaneous delivery one week later.
15. Dossena (Carretti)	1934	W	Young girl		?	
16. Casu	1934	W	31	3	7	Spontaneous delivery, live 7 months' baby. Few hours postoperatively.
17. Carretti	1936	W	32	6	6	Went to term.
18. Spirito	1937	W	31	1	Term	Spontaneous labor. Live fetus prior to onset.
19. Infantozzi	1937	W	38	9	4-5	Aborted at 5 months.

I

OUTCOME	DIAGNOSIS	COUGH	RIGHT OR LEFT	THERAPY
Aborted spontaneously 14 hours after operation.	Suspected hematoma of rectus muscle.	Cough.	Right.	Evacuated.
Petechia of skin of extremities and thorax.	Suspected hematoma of rectus muscle.	Cough.	Right.	Evacuated after labor.
		Spontaneous.	Left.	Evacuated.
Recovery uneventful.	Hematoma of rectus muscle.	Strain of labor.	Bilateral.	Conservative
History incomplete.	Placental hematoma.	Cough.	Right. 12 by 6 by 2 cm.	Evacuated. It had ruptured into peritoneal cavity above and behind.
	Hypernephrosis. Later ovarian cyst.	Severe cough.	Right.	Evacuated clot one week after labor. Clot behind the rectus. Weight, 2 pounds.
Both mother and child lived.	Rupture of rectus muscle.	Labor strain.	Bilateral.	Conservative.
Died of hemorrhage, shock of operation.		Cough.	Left.	Evacuated and tamponade.
	Twisted cyst.	?	Left.	Evacuated.
Died of pneumonia.	Concealed hemorrhage.	Cough. Influenza.	Left.	Evacuated extraperitoneal.
Both mother and child lived.	Hematoma of rectus muscle.	Cough.	Left.	Evacuated and sutured artery and low cervix section.
Woman lived.	Premature separation of placenta	Severe cough.	Right.	Cesarean. 7 months' twins, stillborn, none on hematoma.
Dead fetus. Mother lived. Wassermann 4 plus.	Twisted pedicle of muscle hernia.	Cough.	Left.	Evacuated.
Recovery despite rupture of peritoneal cavity.		Fall.	Right.	Conservative.
Died.		History incomplete.		
1,900 gr. fetus and mother lived.	Extravasation of urine.	Cough. Influenza.	Right.	Evacuated submuscular hematoma.
	Ruptured pregnant uterus. Premature separation of placenta or ovarian tumor.	Cough. Bronchitis.	Right. Ecchymosis palm size lumbar region.	Treatment of surgical shock.
	Ovarian cyst, twisted pedicle postpartum.	Labor strain.	Left.	Laparotomy. 1 liter fluid blood in musculo sac and into broad ligaments.
Recovery.	Pedunculated fibromyoma.	Fall.	Left. Ecchymosis of abdominal wall.	Evacuated. Drainage. Became infected.

TABLE

AUTHOR	YEAR RE- PORTED	RACE	AGE	GRAVIDA	MONTH OF PREG- NANCY	PREGNANCY
20. Jack (Cullen)	1937	N	30+		7-7½	Spontaneous labor at term.
21. Edwards (Cullen)	1937	N	32	8	8	Probably did not abort.
22. Fiaschi (Cullen)	1937	W	Young girl		Term	Delivery spontaneous prior to operation.
23. Handfield-Jones (Cullen)	1937	W		1	7	Delivered just prior to onset. Stillbirth.
24. Hobbs	1938	W	30	6	8½	Undelivered.
25. Ashkar	1939	W	30	8	5	?
26. Perez et al.	1940	W	27	5	Near Term	Stillbirth.
27. Von Massenbock	1942	Not obtainable				
28. Torpin	1943	N	34	12	8	Continued to term. Delivered 8 days after operation.

(b) There appears to be some special tendency to muscle degeneration in typhoid fever and influenza. In pregnancy it may be that the overstretching of the muscle may in some slight way increase its susceptibility to trauma.

It will be noted that in almost all cases of the condition in pregnancy collected and reported here, there was some evidence of trauma either from labor or from coughing or from a fall. Hematoma developed with labor strain in cases of Vogt, Lichenstein, Spirito, Perez et al., Fiaschi (Cullen), and Handfield-Jones (Cullen).

An associated factor in the lesion was trauma of coughing in the cases of: Stoeckel (in two cases), Schroeder, Carnelli, Casu, Lantuejoul, Carretti, Ashkar, Cullen-Edwards, Andrews, Hobbs, Decio, Abelin and Torpin. Hematoma developed following a fall in Brindeau's and Infantozzi's cases.

The pertinent factors in the history and findings of each case from the literature including the case here reported, are listed in Table I. It is to be noted that the condition is more apt to occur in multiparas of thirty or more years of age. The diagnosis is apparently quite simple if the condition is kept in mind. Consequently a wider dissemination of knowledge of the subject should prove useful.

I—CONT'D

OUTCOME	DIAGNOSIS	COUGH	RIGHT OR LEFT	THERAPY
Recovery.	Hematoma of rectus muscle.	History of none.	Right.	Conservative.
Recovery.	Hematoma of rectus muscle.	Severe cough. Felt tearing with coughing.	Left (upper).	Evacuated 500 c.c. clot and ligated bleeding artery.
Probable recovery.	Ruptured or suppurating hydatid of abdominal wall or of left lobe of liver.	Labor strain.	Left.	Evacuated.
Recovery	Hematoma of rectus muscle.	Typhoid fever and labor strain.	Right. Bluish; ecchymosis over coconut sized tumor.	Delivered just prior to onset.
Died of hemorrhage.		Cough.	Left.	
	Twisted ovarian cyst.	Cough. Bronchitis.	Right.	Evacuated.
	Diagnosis undetermined. Exploratory laparotomy.	Labor strain.	Right.	Evacuated.
Mother and infant lived.	?	Cough.	Left. Triangular area of ecchymosis below umbilicus.	Operation without evacuation of clot.

Case Report

M. T., Negro female, aged 34, well developed and well nourished, of medium constitutional type, was admitted to the University Hospital, February 3, 1937, because of an abdominal tumor complicating pregnancy at eight months.

Her menstruation began at twelve or thirteen years of age. The periods were of 8 days' duration, with moderate bleeding, and they were regular. She was married at 16 years of age, and her first child was born 10 months later. Since then she had given birth to one almost every year, so that she had eleven living and one dead (fifth one, female, 6 years old, died suddenly, cause unknown). Her last child before this pregnancy was born October 5, 1935. She states that she never had been ill and never had to stay in bed except for childbirth. All of the children were born at home and with easy labors.

In regard to the present illness, she stated that about two weeks previously, she had developed a cough which was severe enough to cause her to take to her bed and she has been in bed since. After she had been coughing one week, she developed a gradually increasing dull pain in the left side of the abdomen opposite to the umbilicus, "like something pulling and drawing along this side." This was aggravated by coughing. She was coughing at the time she first noticed the pain. Since coming to the hospital the cough and pain have simultaneously abated. She denies a fall, or injury to her abdomen, and she denies attempts at abortion.

Examination.—Temperature 98.6° F., did not rise during her entire stay in the hospital, pulse 78, respiration 18. W.B.C. 7,400, R.B.C. 3,900,000. Hg. 60 per cent, no malaria parasites, P.M.N. 62, P.M.B. 1, lymphocytes 26, monoeytes 9, urine essentially normal, as well as blood chemistry and phenolsulphonphthalein output. Wassermann and Kahn negative, blood pressure 120/80. Physical findings were quite normal except in the abdomen. There was no evidence of focal infection.

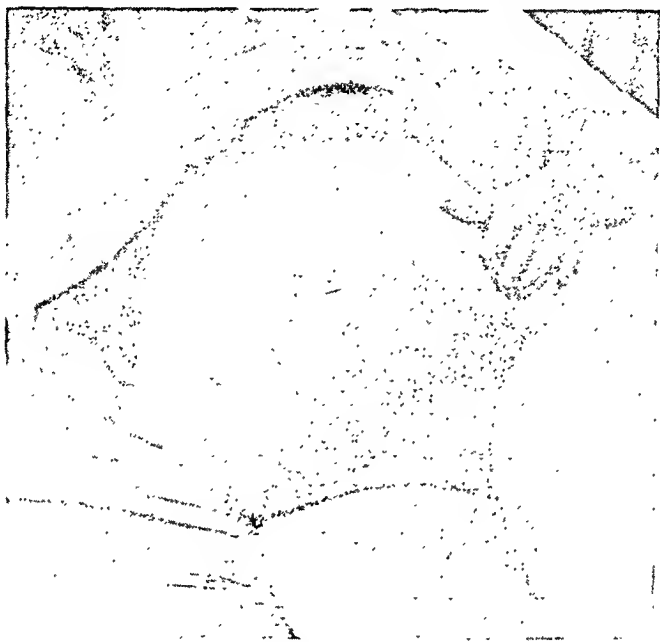


Fig. 1.—Photograph of patient with hematoma of rectus abdominis muscle, showing ecchymosis of the skin below the umbilicus.

Examination of the abdomen reveals the fundus of the pregnant uterus about 28 cm. above the symphysis pubis. Panculus adiposus is of considerable thickness. The abdomen in addition to distension by the pregnant uterus also contains, apparently to the left of the uterus and distinct, a mass the size of a large oval grapefruit, rather firm and tender, appearing like an intra-abdominal tumor. The uterus is pushed to the right by the mass. Percussion of the liver reveals it to be normal in size and position. There is no evidence of hernia. The extremities, glands and reflexes are normal. There is no edema and no rash.

The correct diagnosis was not made, probably because it was not thought of. The following were considered: ovarian cyst, fibromyoma, hydronephrosis and finally after ecchymosis of the skin appeared, simultaneous intrauterine and ectopic pregnancy. The condition being not very disturbing, she was observed for two weeks with interesting results recorded in the daily notes, summarized as follows:

As the bronchial infection subsided, the mass became less tender and she was allowed to walk around. This was followed by a sensation of pressure in the mass which increased in size and became more painful when the fetus moved against it. Finally, late in the second week, there appeared an area of extravasations of blood into the skin below the umbilicus. This increased in size with further increase in the tumor and she developed mild surgical shock with sweating and prostration.

A thorough study of the urinary tract by cystoscopy had revealed both ureters spurting urine in normal amounts and pyclograms showed no hydronephrosis. On the day of the last recorded daily note, because of her symptoms indicating severe hemorrhage, an exploratory laparotomy was done through a suprapubic mesial incision. The whole lower portion of the left rectus muscle was infiltrated with old and new blood clots. No point of active bleeding was located. The pregnant uterus was of normal pink color, not ecchymotic and not contracted. The incision in the abdominal wall was closed well with silkworm-gut tension sutures which were left in until after delivery which occurred one week later. The first stage of labor was 3 hours and 15 minutes; second stage, 3 minutes and the third stage, 10 minutes, a total of 4 hours and 5 minutes. Morphine was given at the onset for fear of bursting the incision. The child weighed 8 pounds and 2 ounces and was normal. Recovery was uneventful and four days after delivery, the hematoma in the left rectus muscle had shrunk to a tumor measuring 11 by 9 cm. and 5 cm. thick. Several weeks later, examination revealed no evidence of a mass in the rectus muscle and there was no herniation. About 2 years later, this patient became pregnant again, but had a spontaneous abortion at two or three months.

Analysis of Reported Cases

Race.—Three only of the 27 cases were in Negro women. However, most of the patients were reported from European clinics where the incidence of Negroes is small. Two of those reported by Cullen were in Negro women.

Age.—Eleven occurred in the half decade of 30 to 34 years. There were three under 20 years of age, three between 20 and 29 years and four after 35 years. The oldest was 40 and the youngest 16 or less. Based upon the incidence of pregnancy in the various age groups as shown in New York by Yerushalmy et al., it is found that the patients with hemorrhage of the rectus muscle fall, as a rule, in the higher age group than that of normal pregnancy.

Gravida.—There were only 3 primiparas in the group. Among the 18 women in whom the number of pregnancies was stated, there were 90 pregnancies, an average of 5 each. This includes the 3 primiparas. Several others not included were noted as being multiparas. Consequently multiparity is a distinct etiologic factor in this condition. Likewise most of them occur late in pregnancy, many of them being near term.

Etiology.—The lesion in practically every case was associated with some degree of trauma. The two outstanding elements of injury were: first, cough, and second, labor strain. The former occurred in 15 cases here and may have been present in some in which the history on the subject was incomplete. Labor strain was noted in 6 cases. A fall was noted in 2 cases. Influenza and typhoid fever were additional factors in one case each. These diseases may have some disabling effect upon the muscle itself. According to Cullen:²³ "Virchow drew attention to rupture of the rectus muscle in typhoid fever and gave a fascinating description of the hyaline or waxy degeneration of the rectus abdominis muscle frequently occurring in this disease. Zenker, in 1863, had an opportunity of making many autopsies on patients dying during a very extensive typhoid epidemic. He described the lesions in this and other

muscles so well that the changes became known as Zenker's degeneration." He also stated that Keen, in his Toner lecture of 1876, "The Surgical Complications and Sequels of The Continued Fevers" described the same condition. Also Hilgenreiner,³⁰ in 1923, found rupture of the recti muscles in 11 of 202 cases of typhoid fever autopsied at the Charity Hospital, Berlin. Similarly in regard to influenza, Cullen quotes among others, Wolbach's pathologic findings in the influenza epidemic at Camp Devens. The lesions described were similar to those found in Zenker's degeneration and were present not only in the recti muscles, which more easily ruptured due to the intense coughing associated with influenza, but also in other muscles of the trunk. Now, it may be possible that other milder conditions may also have a tendency to muscle changes enough to weaken it and make it more susceptible to trauma. It appears that there must be considerable hypertrophy of the recti muscles in every case as the size of the uterus increases in pregnancy. Furthermore, it may be that hypertension may play a part in causing, or at least increasing the size of the hematoma.

Site of Lesion in the Muscle.—In this series, in 12 cases, the lesion was in right rectus, and in 11, in the left rectus, and it was bilateral in 2 cases. In four of the cases there was present an area of ecchymosis in the skin of the abdominal wall over or adjacent to the lesion. In the case herein reported, it developed rather late in the course of the disease.

Therapy.—In the cases reported the treatment has usually involved surgery to the extent, at least, of exploratory operation. Only in such cases could one be certain of the diagnosis. Probably a great number of hematomas of the recti muscles in pregnancy and labor are small, unnoticed and undiagnosed, and consequently unreported. Study of the operative treatment reveals only 2 cases in which the bleeding artery was found and tied. It also shows that operation was followed by abortion in 2 cases (Stoeckel and Carnelli), and was followed in a few hours by premature delivery in the case of Casu. In most of the cases the hemorrhage was limited to the region of the rectus muscle, usually within its sheath. The blood seeped out enough in 4 cases, at least to cause ecchymotic staining of the skin. In one case the hemorrhage escaped the limits of the muscle and extended into the broad ligament, and in one it ruptured into the peritoneal cavity. In 2 incompletely recorded cases, with death from hemorrhage before help arrived, most certainly the bleeding extended beyond the muscular sheath into the peritoneal cavity or into the broad ligaments. Aside from these 2 deaths, 2 other mothers died, one immediately following operation, from hemorrhage and shock, and one 5 days postoperatively from pneumonia. Of course, most of these deaths occurred without the benefit of modern transfusion methods. Most of the other operations were done either frankly as exploratory or to clear the diagnosis, and all that was accomplished was to evacuate a clot. Consequently, the therapeutic measures recommended for this condition are (1) correct diagnosis, (2) rest in recumbent position, including relief of intermittent strain of coughing, or of labor by proper sedation, tight abdominal binder and ice bag, (3) blood transfusions to replace loss and prevent surgical shock, (4) possible administration of blood coagulants.

Diagnosis.—The most important item seems to be to keep the possibility of the condition in mind. I am of the opinion that, while it has

not been done to my knowledge, a lateral soft tissue roentgen film should reveal a localized tumor mass anterior to the outline of the uterus. Furthermore, ecchymosis in the abdominal wall in the neighborhood should be quite pathognomonic. Of great help in the diagnosis is the fact that in the great majority of cases, there is some history of trauma, cough, labor strain, fall, etc.

Mortality.—Assuming that all women lived except those definitely reported to have died, the maternal mortality of four gives a rate of about 15 per cent. The data in regard to the fetus is less complete, but probably half of them perished. Consequently, this condition ranks in danger with the other hemorrhages of the third trimester.

Summary

So-called spontaneous hematoma of the rectus abdominis muscle was found to occur in both white and Negro women. Primary etiologic factors were trauma of cough, labor, strain, or rarely, external injury. Other primary factors were rarely muscle degeneration from typhoid fever or influenza. Secondary etiologic influences were age, multiparity and terminal stages of pregnancy. There was no preference for right or left side involvement. A few ruptured the muscle sheath and extended into the broad ligament or into the peritoneal cavity. These, as a rule, furnished the fatal cases. A few were accompanied by skin ecchymosis.

From a study of these cases, it is concluded that proper conservative therapy is indicated; chief of these includes early diagnosis, complete rest, and blood transfusions where indicated. Lateral soft tissue roentgenography is suggested for aid in diagnosis. The maternal mortality was 15 per cent and the fetal much higher.

The lesion should assume its rightful place as a dangerous hemorrhagic catastrophe of the third trimester of pregnancy.

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PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA

A Study of 93 Cases*

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THE greatest single factor in maternal mortality is hemorrhage with its attendant shock. The role played by premature separation of the placenta, with its incipient or explosive onset, with its clinical picture sometimes changing rapidly and the prognosis always doubtful is, by virtue of these factors, one of the most treacherous and at times the most tragic of obstetric complications.

From September, 1932, to January, 1942, at the New York Lying-In Hospital, there was a total of 32,434 deliveries including the outdoor service. In this series there were 93 cases of premature separation of the placenta, an incidence of one in 348 cases. There were three maternal and 49 infant deaths. In the management of these cases there was no fixed rule as to how delivery should be effected since this was left to the judgment of the physician attending the patient. Four hysterectomies were done on patients who had been delivered by cesarean section. One of these, however, was performed for multiple fibromyomata and not for flaccid uterus.

Table I presents the details of this series of cases.

Treatment

It is generally agreed that patients with premature separation of the placenta are unquestionably better treated in a hospital, where they can be promptly typed and matched for transfusion and where blood is made available as soon as the necessity for it arises. Beyond this there is some disagreement as to just how these cases should be treated, particularly as to the method of delivery.

The "radical method" prescribes that all cases should be delivered by cesarean section, the advantages being that there is a greater chance of obtaining a live baby; furthermore, the operator has a better

*Read, by invitation, at a meeting of the New York Obstetrical Society, March 9, 1943.

opportunity to note the extent of the damage to the uterus and consequently, is in an ideal position to remove the uterus should it fail to contract. On the other hand, the conservative school offers some excellent figures to bolster their contention that conservatism as a rule offers the best results as regards maternal mortality.

TABLE I. CASES OF PREMATURE PLACENTAL SEPARATION AT THE NEW YORK LYING-IN HOSPITAL

SEPTEMBER 1, 1932, TO JANUARY 1, 1942			
TOTAL DELIVERIES			32,434
Premature separation of Placenta	93 (1 in 348)	0.28%	
Maternal deaths	3	3.2%	
Infant deaths	49	52.7%	
Primigravida	25	26.5%	
Multigravida	68	73.5%	
Hemorrhage {Concealed	17	17.2%	
{External	76	82.8%	
Type of delivery {Cesarean	38	40.0%	
{Pelvic	55*	60.0%	
Toxemias	21	22.5%	
Hysterectomies†	4	4.3%	

*1 Hysterectomy done for fibromyomata.

†1 Patient died before delivery.

Solomons,² at the Rotunda Hospital in Dublin, in 1933 reported a maternal mortality rate of only 3.5 per cent.

Irving,¹³ in 1937 reported a mortality of only 5.1 per cent. In the same paper he reported a mortality rate of 14 per cent on cases of concealed hemorrhage delivered by cesarean section. He stresses the point that if toxemia is present and the hemorrhage is concealed, the prognosis is much worse. This combination of factors in general is accepted to be true.

That progress has been made in the treatment of this serious obstetrical complication is evident when one compares some of the statistical reports published in the past twenty-five years with those of forty and seventy years ago. For example, Harrar⁷ in 1917 reported a mortality rate of 8.7 per cent; Solomons,² 1933 of 3.5 per cent; Irving,¹³ 1937 of 5.1 per cent, whereas Holmes²⁴ report in 1901 was 32.2 per cent and Goodell³ in 1870 was 50.9 per cent in concealed hemorrhage cases.

As one contrasts the reported mortality rates of the older writers with those of the more recent ones, there are certain facts which become evident and explain in part why the results have been improved. Today most patients with premature separation of the placenta are hospitalized. The beneficial effects of blood and plasma transfusions are made readily available, a life-saving measure which the earlier physicians could not take advantage of as we do now. Cesarean section is employed more liberally in the severe cases before too much

TABLE II. COMPARATIVE MORTALITY RATES

GOODELL	HOLMES	HARRAR	SOLOMONS	IRVING	O'REGAN
1870	1901	1917	1917	1937	1942
50.9%	32.2%	8.7%	3.5%	5.1%	3.2%

damage has been done to the uterus. We have learned to respect the cervix more and to discourage accouchement forcé. And in the final analysis, it was the heroic treatment in the earlier days of women with premature separation of the placenta, many of whom were in more or less severe shock to begin with, that was responsible for many deaths rather than the premature separation itself.

At the present time most clinics follow a "middle of the road" course in treatment and are guided by their experience and the clinical picture of the case when it comes under their care. If the obstetrician elects to treat a patient conservatively he may have to change to radical measures should a change in the clinical picture make it imperative that he do so.

In the conservative treatment the bag is dangerous as it may convert the case into what practically amounts to a concealed hemorrhage. The use of some form of pressure binder, whether it be the windlass or the Beck type, is a valuable adjunct in the ante-partum treatment of these cases.

Most fatal cases of premature separation of the placenta die post partum of hemorrhage and shock. An analysis of them frequently reveals that the operator temporized too long and was not in a position to do an immediate laparotomy. On this basis it seems logical that all cases of premature separation where vaginal delivery is contemplated and particularly where symptoms are severe, delivery is better effected in an operating room that has been set up for laparotomy, or in a delivery room with operating facilities close by immediately available. This would eliminate time loss and blood loss should hysterectomy be necessary. It is evident that this procedure would reduce the maternal mortality rate and justify the means to attain it.

Summary

At the New York Lying-In Hospital (outdoor service included) from September 1, 1932, to January 1, 1942, there were 32,434 deliveries. In this group there were 93 cases (incidence 1 to 348) of premature separation of the placenta. There were 3 (3.2%) maternal deaths, one intrapartum and two postpartum. There were 49 (52%) infant deaths.

All cases of premature separation of the placenta where pelvic delivery is contemplated and particularly if symptoms are severe, should be delivered either in an operating room that has been set up for laparotomy or in a delivery room with operating room facilities close by, immediately available, thereby eliminating time loss and blood loss should hysterectomy be necessary.

Fatal Cases

Case 1.—Admitted March 6, 1936. False labor, mild toxemia. 10:30 P.M. patient in labor with strong pains. Delivered spontaneously after labor 4 hours 8 minutes. After delivery of head there was 200 c.c.

blood loss. After delivery there was profuse hemorrhage. Uterus packed. Pulse 120. Blood pressure 140/90. Hemorrhage controlled for an hour. Uterus repacked. Glucose 10 per cent given while transfusion made available. Blood transfusion 300 c.e. given but patient went into severe shock and died 2 hours 45 minutes after delivery.

Case 2.—Multigravida at term. Admitted June 22, 1937. Induced castor oil enema and nasal pit (2 + 7). Intrapartum convulsion. No toxemia. Slight antepartum bleeding during labor. Total labor 4 hours 47 minutes. Pains severe just before delivery. Delivery normal. Patient in shock following delivery. Uterus failed to contract; bleeding quite profuse. Exploration of uterine cavity revealed no rupture. Uterus packed. Glucose 10 per cent 400 c.e. given while awaiting transfusion. Patient died 1 hour 13 minutes following delivery of placenta. Total blood loss 1,200 c.e.

Case 3.—Multipara. Toxemia. Blood pressure 225/130. Admitted June 24, 1934 with low back pains and irregular vaginal bleeding. No clots. 6/25/34 A.M. patient in labor. Uterus did not relax well between pains. At 4:00 P.M. Voorhees bag inserted. Some bleeding noted from rupture of varix near urethra which was controlled by 1 suture. Following bag insertion patient became worse. Given glucose 10 per cent 500 c.e., also 500 c.e. blood. Two hours later second transfusion of 500 c.e. given but patient's condition became rapidly worse and she died undelivered.

Autopsy.—Area of discoloration lower uterine segment. Large retroplacental clot 500 c.e.

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791 PARK AVENUE

UNUSUAL DECIDUAL REACTION OF THE CERVIX

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EXAMINATION of the cervix at stated intervals during pregnancy will reveal marked changes in consistency, form and position. Within a few weeks after conception, there will be softening of the tip increasing upward toward the corpus and from without inward. This softening is caused by imbibition of the tissues and increased vascularity, both hemic and lymphatic.¹ With increased anteflexion of the uterus, the cervix points forward and the uterus as a whole, sinks lower in the pelvis. The imbibition of the epithelium often leads to erosions and proliferation of the cervical epithelium. Catarrhal affections of the cervix are much exaggerated, often causing marked leucorrhea. If the patient previously has had cervicitis with erosions, the condition may become severe enough to require treatment for spotting of blood and profuse irritating discharge.

The question arises, as to why in certain cases the proliferation of the cervical epithelium is barely noticeable, while in others, it represents a prominent feature of the cervical structure in the pregnant woman. Hoffbauer² considers that the occurrence of deciduallike connective tissue cells in a certain proportion of cases attests to enhanced pituitary activity. Keiffer and Devraigne³ state that the cervical mucosa plays no part in the nutrition of the ova but, on account of the presence of the ova and the rich vascularization which this entails, it does undergo a certain degree of hypertrophy; its glands increase in size and their secretion is much exaggerated. The product of their secretion forms the mucous plug which serves as a protective organ against the vaginal flora. At the internal orifice, there is a zone of transition with the mucosa of the inferior segment. The cervical mucosa does not form a deciduous membrane; it does not exfoliate after labor. Nevertheless, it is true that there is sometimes a very definite deciduous reaction in the cervical mucosa, and that it may be transformed into decidua serotina, as is proved by the reported cases of isthmic and cervical placentas. Latzko⁴ states that decidual reaction is rarely seen in the cervix although sometimes observed in connection with polyps, in which case there is much evidence of inflammation. Stieve⁵ reports specimens showing evidence of epithelial activity such as reduplication of layers, vacuole formation, and some vascular polymorphism of the nuclei. The beginnings of these changes could be traced to the fourth month of pregnancy. A striking feature of his studies is the occurrence of such changes in discrete localities, the remaining epithelium retaining its original character. The changes in the human cervix during gestation are interpreted as an indirect metaplasia and, under the influence of certain stimuli, may resume their embryonic potentialities. Whether this response of the cervical epithelium to the stimulus of pregnancy may become a predisposing factor of clinical importance for late cancer development is still being studied.

The object of this communication is to report a case in which the cervical tissues showed an unusual decidual reaction. It is hoped that the observation may be of some value in the constant effort which is

being made to clarify the early differential diagnosis of malignancy of the cervix.

Case Report

Mrs. M. Me., white, aged 46 years, gravida vi, para v, had a history of three operative and two normal deliveries and one spontaneous miscarriage at sixteen weeks. In July, 1939, a vaginal plastic was performed, anterior and posterior colporrhaphy (Maneheimer operation). The postoperative course was uneventful. She was first seen by me on October 22, 1942, at which time she was uncertain whether she was pregnant, or whether her condition was due to a tumor or to the menopause. Her last menstrual period occurred on July 4, 1942. She had

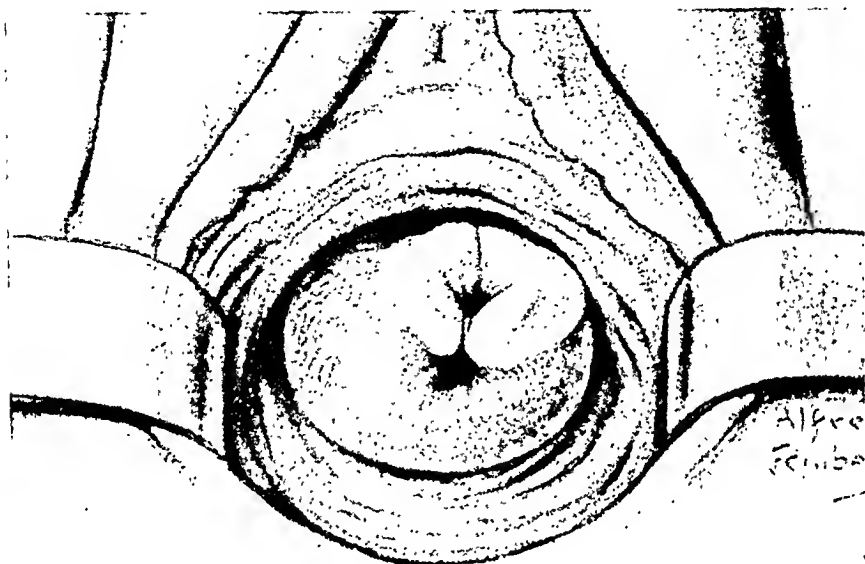


Fig. 1.—Showing unusual softening of cervix with raised dull, glistening vesicular area.

been to a clinic where, owing to a negative Aschheim-Zondek test, she had been told that she was not pregnant and that she probably had a fibroid tumor. Physical examination showed a well-developed, well-nourished woman. Her blood pressure was 166/96. The Wassermann reaction was negative. Further general examination, including urinalysis, gave negative results. Vaginal examination revealed a firm pelvic floor and normal vaginal walls. The cervix showed an area of unusual softening in the region of 12 to 2 o'clock and inspection revealed a raised dull glistening vesicular area resembling a small new growth which bled easily on palpation. Believing it to be an early cancerous lesion, a biopsy was made. The uterus was enlarged to approximately the size of a four months' pregnancy and was slightly irregular in shape, due to a small fibroid, 3 cm. in diameter, in the right horn. The patient developed a mild toxemia near term and was delivered at 38 weeks, by a classical cesarean section, of a living male child weighing eight and one-half pounds. The post-partum period was uneventful. Fig. 1 shows the gross appearance of the cervix.

Pathologic Report (by Dr. A. Rottino).—Macroscopic. The specimen consists of a small nondescript piece of tissue, solid, gray in color, weigh-

ing less than one gram. *Microscopic.* On section, the tissue is found to be very cellular (Fig. 2). The surface mucosa has desquamated. Scattered throughout are irregular glands of moderate size, lined by epithelium which varies from flat to columnar (Fig. 2b). For the most part it is simple. Only in parts are the cells piled up three and four deep. In an occasional gland the epithelium is thrown up into folds. Between the glands are compactly arranged cells, large, irregular in shape, with abundant eosinophilic cytoplasm (Fig. 2a). Their nuclei vary from oval to round. Blood vessels are present in moderate numbers, dilated and congested. Here and there collections of polymorphonuclear leucocytes about thrombosed blood vessels are visible. *Diagnosis.* Cervical tissue showing an unusual decidual reaction.



Fig. 2.—Biopsy showing tissue to be very cellular with marked decidual reaction.

The microscopic findings in this tissue are most unusual for the cervix. In a rare biopsy of the cervix, taken from a pregnant woman, I have observed swelling of the stroma cells but never anything to approach the change which has taken place here.

Summary

A case of unusual decidual reaction of the cervix has been described. The importance of differential diagnosis of rare lesions of the cervix has been emphasized. That the changes in the cervix during pregnancy are not constant and typical is not surprising when we recall the various sizes and shapes of cervixes encountered in the routine of obstetric examination.

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THECA CELL TUMOR OF THE OVARY AND CARCINOMA OF THE ENDOMETRIUM

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SINCE the first description of theca cell tumors of the ovary in this country by Melnick and Kantor¹ in 1934, many reports have followed, describing it as one of the variants of benign solid tumors of the ovary with hormonal potencies. However, some of the theca cell tumors have shown in addition features resembling granulosa cell. The association of theca cell tumor and carcinoma of the endometrium is extremely rare. There have been two cases reported; Porter and Bramhall's² case was a 72-year-old white female, with uterine bleeding for 2 years, and Dockerty's³ case was 58 years of age and was encountered in a series of 10 cases of theca cell tumors. Dockerty noted 3 cases of carcinoma of the endometrium in 32 cases of granulosa cell neoplasms while Stohr⁴ has also reported 3 cases. Thus the incidence of carcinoma of the endometrium has been twice as frequent in cases of granulosa cell tumors as in theca cell.

Theca cell tumor usually manifests itself past the menopause and exerts a specific biologic function in elaborating an estrogenic hormone which induces uterine bleeding. This bleeding simulates menstruation although the periods are irregular and prolonged. Except for bleeding, the patients feel fine and following removal of the ovarian neoplasm there is a cessation of the bleeding and often changes in their general well-being. These patients frequently are not grateful to the surgeon for having been operated upon, because the cessation of the estrogenic hormone makes them feel old. The theca cell neoplasm may therefore be considered as a rejuvenating type of tumor.

The changes in the endometrium in theca cell tumors are quite characteristic of the elaboration of the estrogenic hormone. The glands become markedly proliferated and often show cystic dilatation (so-called Swiss cheese variety).

The transformation of the endometrium from the abnormal physiologic to the malignant phase is possible under the influence of continuous estrogenic stimulation.

The case to be reported was diagnosed clinically as fibroid uterus and the theca cell tumor of the ovary and the carcinoma of the endometrium were incidental findings at operation.

Case Report

Patient E. J., aged 55 years, was admitted to the hospital with complaints of vaginal bleeding for 18 months and abdominal pain for one year. She stated that she had past through the menopause 10 years before. During the past 18 months she had noticed attacks of vaginal bleeding lasting 2 or 3 days and often recurring in 2 or 3 days. This had been associated with abdominal pain in the right lower quadrant during the past year. She had had 5 children and one miscarriage at 3 months.

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Her menstrual history had been normal. Onset at 13 years, duration 3 days every 28 days, with a scanty flow.

The blood pressure showed a slight hypertension, 154/90.

In the abdomen a mass was felt rising out of the pelvis and extended up to the umbilicus. It was firm, freely movable and not tender. Vaginal examination disclosed active bleeding and the corpus uteri was incorporated in the abdominal mass.

The clinical diagnosis was fibroid uterus.

A supracervical hysterectomy and bilateral salpingo-oophorectomy was performed.

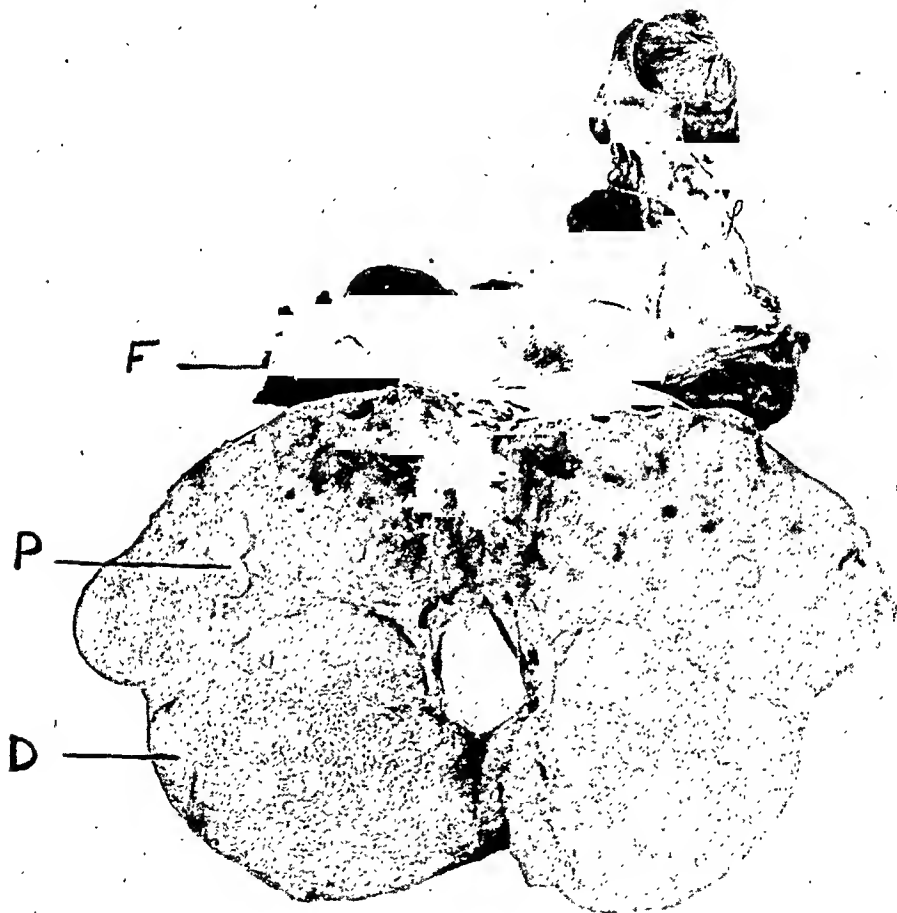


Fig. 1.—Photograph of the tumor sectioned in half. The dark discoloration of the tumor (D) is due to its imbibition with sudan III. Note the plaques of fibrosis and hyalinization (P). (F = Fallopian tube.

Pathological Report.—The specimen was a uterus amputated above the cervix measuring 14 by 11 by 15 centimeters and was deformed by subserous, intramural and submucous firm nodes up to 13 centimeters in diameter. The nodes on sectioning were pink and trabeculated. The endometrium was markedly thickened, injected purple-red and attached to it were several pedunculated soft polyps up to 5.5 centimeters in largest diameter. One of the polyps was very soft and friable. One of

the ovaries was enlarged, firm and measured 5.5 by 4 by 3 cm. The surface was encapsulated, slightly nodular, and yellowish-tan in color. On sectioning the light yellowish-brown color was striking and the surface appeared trabeculated. Attached to the ovary was a slightly thickened patent Fallopian tube. The other tube and ovary were unchanged.

Half of the ovarian tumor was submerged in sudan III for twenty minutes (see Fig. 1). Most of the tissue turned into a bright orange. On the section surface there were discrete dense white areas of fibrosis and hyalinization, a finding rather characteristic of theca cell tumors.

Sections from the ovarian tumor revealed it to be composed of dense bundles of spindle-shaped cells containing regular oval nuclei. Scattered about were areas of fibrosis and hyalinization. Sudan III stain revealed the vacuolar cytoplasm to be rich with fine lipid droplets (Fig. 2). Scattered about the stroma, there were also a sprinkling of fine lipid droplets.

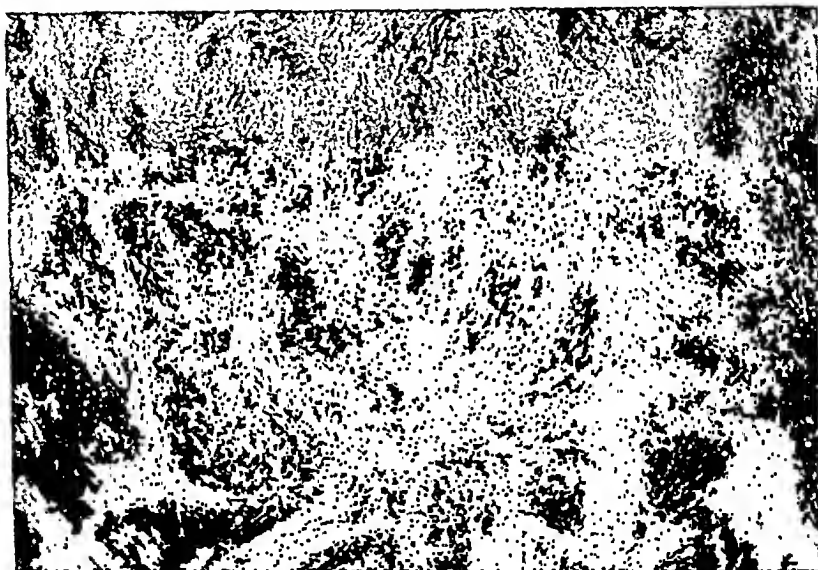


Fig. 2.—Photomicrograph of a section of the tumor stained with sudan III. The cells are arranged in bundles rich in lipid. Scattered about are characteristic fibrous and hyaline plaques devoid of any lipid material.

Sections from the endometrium in the region of the friable polyp revealed active proliferating glands with dilated lumina. They were lined by several rows of columnar cells with irregular large hyperchromatic nuclei. There were many atypical mitotic figures seen. The stroma was composed of a thin fibrillar septa infiltrated with small foci of round cells (Fig. 3). The glands showed beginning invasion of the myometrium.

Diagnosis.—Theca cell tumor of the ovary, adenocarcinoma of the endometrium and fibromyomata uteri.

Discussion

Theca cell tumors of the ovary are solid, benign and occur usually past the menopause. They are rich in lipid material and usually can be identified by the yellow discoloration. This material is double refractile and is either cholesterol or cholesterol esters. These tumors

elaborate an estrogenic hormone and cause a physiologic hyperplasia of the endometrium. That the physiologic hyperplasia may become abnormal and progress to a neoplasm is illustrated in this case.

In a patient past the menopause, who manifests periods of uterine bleeding, and if the uterine scrapings are negative for malignancy a theca cell tumor of the ovary should be considered.



Fig. 3.—Photomicrograph shows the glandular arrangement of the carcinoma of the endometrium.

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FULL-TERM ABDOMINAL PREGNANCY*

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ADVANCED ectopic pregnancies going to full term or beyond most frequently begin as a tubal pregnancy that secondarily develop into the abdominal cavity. The fetus may rarely in this type of extra-uterine pregnancy continue to develop after tubal rupture, but much more frequently a fetus growing in the abdominal cavity was aborted or extruded through the fimbriated end of the tube but retained its original connection and added many newer adhesions. Thus one frequently has to deal with very vascular connections to the contiguous pelvic organs, bowels and omentum. The following case is reported not only for its rarity but also for its typical clinical history and careful work-up of the case.

J. H., Negress, aged 27 years, had one previous pregnancy that terminated early and uneventfully as a spontaneous abortion. The last regular menstrual period was about July 15th, 1941. During the latter part of September of that year she had an episode of very severe pain in the right lower quadrant that subsided spontaneously in about two days. Thereafter pregnancy appeared to the patient to be uneventful; the abdomen grew larger in a normal fashion. Life in the fetus was felt at the usual time (the exact date could not be recalled). In the mid-portion of April she had what appeared to be laborlike pains and vaginal bleeding which ceased spontaneously, and she was discharged from another hospital with the apparent impression that a threatened premature labor had subsided. She was told to return when the pains recurred.

The patient noted when she reached home that the perception of life movements ceased permanently. For a brief period her breasts contained milk. Then the size of her abdomen became smaller and she lost weight. She had a menstrual period in July, August and September and was admitted to the obstetric service of the Cook County Hospital on October 7th, 1942. Her chief complaint was pressure on the urinary bladder, causing her to have frequency and urgency. The patient had the impression that the abdominal mass was causing her to have constipation.

Bimanual examination revealed the following: the uterus was normal in size and consistency and was felt distinctly separated from the abdominal mass which arose from the pelvis to two fingers above the navel, and directed more toward the right side of the abdomen. It was regarded as an abdominal pregnancy.

Lipiodal x-ray showed that the uterus was empty and separate from the fetal skeleton (Fig. 1). The patient's temperature and pulse rate were constantly normal before the operation. On October 15th, the abdomen was opened and the contents carefully observed and sketched. (See Fig. 2.) As the right tube was traced distally, it flared out toward the fimbriated end like a horn. At this region there was a narrow circular ringlike depression and the fetus with its placenta emerged at this site. Through the translucent amniotic membrane the fetus was discernible.

*Presented at a meeting of the Chicago Gynecological Society, April 16, 1943.

There were definite adhesions of bowel and omentum to the amniotic membrane. The latter was incised and the fetus removed. The placental tissue was easily separated from the adherent bowels, omentum, and the posterior wall of the uterus and right broad ligament. There was no problem concerning hemostasis. The left tube was enlarged, apparently a chronic hydrosalpinx. The right tube was removed together with the placenta. The fetus measured 19 cm. crown-rump length. The digits of the left hand and leg were adherent to the amnion and both feet appeared club-shaped.



Fig. 1.—X-ray of pelvis. The lipiodal fills the uterus; the fetus (extrauterine) shows marked overlapping of the cranial bones.

The patient was returned to her bed in very good condition and on the tenth day was allowed up. Her course was afebrile up to this day. That night her temperature had risen to 102.4° F., and two days later reached 103.4° F. Her pulse was 134. Thereafter the pulse ranged between 90 and 120 per minute and her temperature between normal and 100.4° F. A mass could be palpated rising from pelvis to almost the level of the navel. The patient signed her release on November 20th, and was not seen nor heard from for a period of six months. She was examined at that time and all we could find was some residual pelvic inflammation centered chiefly around the left tube. She was able to get about without any discomfort and was referred for pelvic heat treatments.

In summary of this abdominal pregnancy, the patient had a typical clinical course. In the first trimester an episode of severe pain was very

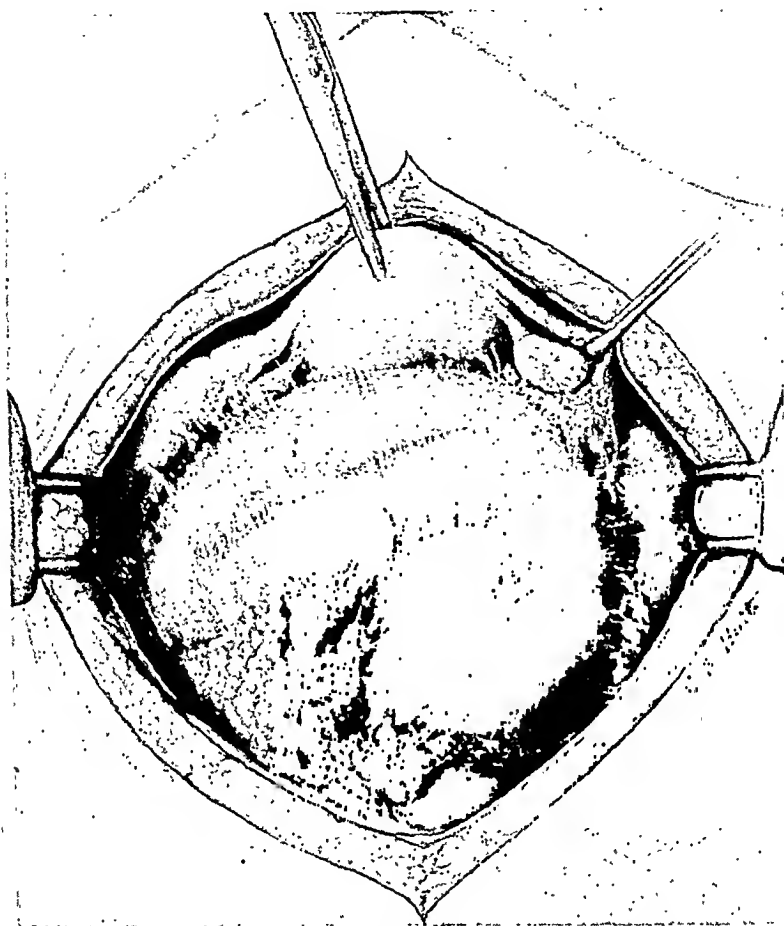


Fig. 2.—The pelvic structures. The left tube appears enlarged by a chronic inflammation, and the intra-abdominal fetus is within the amniotic sac. There are numerous adhesions wherein the amniotic sac and the placenta are fastened to the omentum, small bowels, and the pelvic structures.

likely due to the tubal abortion. At almost full term, she had a spurious labor which ceased spontaneously, and at that time the fetus apparently died. She fortunately did not develop any sepsis. When seen by us she had a fifteen months' gestation. The placenta would not have been disturbed in any way if this patient were seen when the fetus was alive or recently after the fetal death. The period of six months following the death of the fetus permitted the adhesions to become devascularized and rendered the contemplated removal of the placenta safe.

7 ADVANCED UNRUPTURED TUBAL PREGNANCY

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WHILE tubal conception is, in itself not rare, unruptured tubal pregnancy of long gestation periods is so sufficiently uncommon that an instance of one of six and one-half months' gestation may be of interest. Tubal conception usually terminates in a variety of ways in the second or third month, but occasionally a conception may, for reasons as yet undetermined, continue and even come to full term in this location. A few such cases have been reported in the literature. Miller¹ reviewed the previously recorded cases and reported a full-term right-sided tubal pregnancy in which the fetus weighed $4\frac{3}{4}$ pounds and measured $21\frac{1}{2}$ inches. The fetal sac, the Fallopian tube, was exceedingly thin in many places, and measured in its thickest portion no more than 0.5 cm. Microscopically, the wall of the sac consisted of fibromuscular tissue. Its mucosa showed evidence of chronic inflammation and a decidual reaction in both tubes, particularly in the right. The uterus was enlarged to the size of a three months' pregnancy. The preoperative diagnosis had been a breech presentation. In the discussion which followed, several other somewhat similar cases were reported by the commentators.

Schumann² described an instance, in a young woman, aged 22, where the pregnancy reached full term and was thought to be uterine in location. Just before delivery, she began to experience violent pains in the abdomen with excessive fetal activity. The latter suddenly ceased at the end of an hour. Under the mistaken diagnosis of abruptio placenta, the patient was operated upon and an unruptured left Fallopian tube was found, containing a well-formed fetus, which weighed 6 pounds, 14 ounces. The wall of the Fallopian tube was generally thin, measuring only 0.5 cm. in most regions. Microscopic examinations of the excised tube showed a markedly hypertrophied muscular layer and a thin decidua.

Since these case reports, there have been recorded, particularly in the foreign literature, a very occasional similar instance of late and even full-term unruptured tubal pregnancy.³ The case reported here is that of a young woman, L. W., aged 27. Menstruation began at $14\frac{1}{2}$ years, 30-day interval, duration 6 days. Last period July 17, 1942. expected date of confinement April 30, 1943. Fetal movements noted January 3, 1943. She had had 2 miscarriages. Physical examination was essentially negative. Blood pressure, 110/70. Two days before her admission to the hospital, on Jan. 31, 1943, she began to complain of pain in midabdomen and about the shoulders. At this time, she was in the estimated $6\frac{1}{2}$ month of her pregnancy. A tender abdominal mass, presumably the uterus, was palpable. Under the mistaken diagnosis of a premature separation of the placenta, the abdomen was opened. A large quantity of dark blood was found free in the peritoneal cavity, and a large mass occupied the pelvis. The latter proved on examination to be an unruptured left Fallopian tube. Hemorrhage

*Read at a meeting of the Philadelphia Obstetrical Society, April 1, 1943.

was coming from the fimbriated end. The uterus was enlarged to the size of a two months' pregnancy. The excised specimen, the left Fallopian tube, was globular and measured 14 by 11 cm. It weighed 1,260 Gm. The fimbriated end was hemorrhagic. Through the fimbriated end, there bulged the head of a well-formed fetus. The wall of the Fallopian tube in some regions consisted of a firm, fibromuscular tissue and measured 0.4 cm. in thickness. Other portions of the wall were exceedingly thin, measuring only 1 mm. Histologically, the tube showed hypertrophied muscular layers and a decidual reaction.

This case is of interest because it reports an exceedingly rare condition and because like several others of a similar character, the correct diagnosis remained in doubt until operation revealed its true nature. Like others previously reported, it also illustrates the potentialities that the Fallopian tube possesses of distending to a magnitude sufficient to contain so large a mass without rupture.

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2019 PINE STREET

SEVERE PRE-ECLAMPSIA WITH SEPARATION OF THE RETINA

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THE occurrence of retinal separation in eclampsia has been noted on several occasions. Its appearance in severe pre-eclampsia is extremely infrequent and is the reason for the reporting of the following case.

Mrs. P. B. (Hosp. No. 142522), a 33-year-old gravida ii, para 0, was admitted to the Bronx Hospital on January 30, 1943, with the following history. Her previous pregnancy in 1939 terminated in a spontaneous abortion in the second month. Her last menstrual period with the present pregnancy was on May 20, 1942. The date of expected confinement was February 27, 1943.

The patient was first seen in the fourth month of gestation. Examination revealed normal pelvic measurements. The heart and lungs were normal. Blood pressure at this time was 120/60. The urine was normal. The patient was seen at regular frequent intervals during which time her blood pressure and urine examinations failed to show any deviation from the normal. On January 19, 1943 the blood pressure was 110/75 and the urine was normal.

On January 30, 1943 the patient was seen at home because of the history of nausea and vomiting of twenty-four hours' duration. This she had attributed to a dietary indiscretion. That morning she had experienced an episode of temporary blindness which lasted about five minutes. Examination at this time showed the presence of marked edema of the face, conjunctivae, hands, legs, and ankles. The patient appeared drowsy. The blood pressure was 195/110. The patient was immediately referred to the hospital.

A urine examination immediately after admission showed solid albumin and microscopically the presence of hyaline and granular casts. The patient was given one-quarter of a grain of morphine sulfate. Sucrose, 50 c.c. of the 50 per cent solution was given intravenously. The following morning Karell diet and the Strogonoff treatment were instituted. The blood pressure was now 180/110. Urine examination showed four plus albumin again together with hyaline and granular casts. An ophthalmoscopic examination indicated the following: The right eye showed a large retinal detachment on the nasal half of the fundus. There was also a small detachment below the optic nerve. The left eye showed a large retinal detachment above and a small retinal detachment below the optic nerve. The retina and the margins of the optic nerves of both eyes appeared edematous so that the margins of the optic nerves were blurred. The retinal arteries were narrowed. The retinal detachments and the edema of the retina were probably due to subretinal and intraretinal transudates. It was felt that the uterus should be emptied at once.

Because of the eye findings, the blood pressure of 195/110, the presence of a thick, elongated, and closed cervix it was decided to deliver the patient by cesarean section. Under spinal anesthesia a living 5-pound female child was delivered by the classical type of operation.

Following delivery the blood pressure was 170/90. On the second day post partum the ophthalmologist reported that the edema of the retina was subsiding but that the retinal detachments were about the same size.

The patient had an uneventful puerperium during which her blood pressure dropped to 150/80. The blurred vision cleared completely and the patient was discharged from the hospital on the twelfth postpartum day. The diagnosis on discharge was pre-eclampsia, severe.

Six weeks post partum the ophthalmologist reported complete recovery from the retinal detachments. The patient's blood pressure was now 120/80 and the urine was normal. Three months post partum the patient was again seen and the blood pressure was 120/80 and the urine was free of albumin or other abnormal findings.

This case is reported because of severe pre-eclampsia with the serious condition of retinal separation as a complication. The complete recovery from this condition after termination of pregnancy by cesarean section is also noteworthy.

FATAL STAPHYLOCOCCUS BRONCHOPNEUMONIA FOLLOWING RITUAL CIRCUMCISION

LOUIS W. SAUER, M.D., EVANSTON, ILL.

J. B. was born on December 1, 1942. His weight was 3,628 Gm. (8 pounds). Initial examination revealed no defects. The mother was unable to nurse for lack of milk. On the fifth day, a sterilized, evaporated milk formula was given; first as complementary, then as supplemental food. On the seventh day, the bleeding time (Duke's method) was 45 seconds; the coagulation time (Lee and White's method), 2 minutes and 15 seconds. Ritual circumcision was performed by a mohel, in the hospital, on the ninth day. The umbilical cord dropped off on the tenth day. On that day a tightly bound, blood-soaked bandage was removed, aseptically, by a nurse. This was accompanied by rather profuse oozing of blood. A sterile gauze bandage was applied, but not as tightly as the original. The infant was apparently well while in the maternity nursery, but gained weight rather slowly. There had been no fever, stools were normal, and the weight was 3,350 Gm. (7 pounds 6 ounces) on the tenth day, when mother and infant left the hospital.

On the thirteenth day, the rectal temperature was 103.2° F. The infant was pale. There was no cough; anorexia was marked. The heart, lungs, abdomen, throat and ears were found to be normal. The weight had not increased. The circumcision wound was definitely infected. When the pus was wiped away from the glans with sterile gauze, a slight defect at the corona could be seen. Apparently the circumcision blade had accidentally cut away a slight amount of the glans penis. The infection seemed to center at this point. In the abdominal wall, about one centimeter above the base of the penis a subcutaneous, slightly elevated, rather hard, movable gland, smaller than a pea could be seen and palpated. Sulfathiazole ointment (5 per cent), spread on sterile gauze, was applied to the penis and changed frequently each day. Sulfadiazine, 0.12 Gm., was given in a teaspoonful of food 4 times daily for three days. Water, sweetened with saccharin, was offered between feedings, and at night when awake. The temperature dropped to normal within three days. Anorexia persisted, but clinical signs were absent. There was no cough. The infant was not examined thereafter. At midnight on the eighteenth day of life, several cubic centimeters of blood and mucus were vomited, spontaneously, and the infant expired before medical aid arrived.

The only necropsy findings were: multiple (over fifty), sharply demarcated, grey abscesses (3 to 10 mm. in diameter), distributed throughout the lungs. The circumcision wound had nearly healed. The palpable gland, noted above, had disappeared. Pus, taken from one of the aseptically incised lung abscesses, showed on direct smear, many single, gram-positive cocci; there were no chains. Capsule stain showed no encapsulated organisms. Culture showed *Staphylococcus aureus* in pure culture.

An infected circumcision wound and accidentally incised glans penis were the portal of entry for this fatal staphylococcal blood-born infection of both lungs.

Editorial

OBSTETRIC STANDARDS UNDERVALUED

IT MAY be stated as a proved fact that the efforts to provide safe care in maternity have been crowned with success if we measure this by the marked reduction in mortality rates which has been prevalent in recent years throughout most of these United States. Improvement in standards concerned with doctors, nurses, hospitals, and public health services, whenever and wherever applied, has saved undoubtedly the lives of many mothers and babies. It is a record of which this country may well be proud.

The participation by the United States in the global war has called for the institution of health measures affecting our entire population, prominent among which is the care of prospective mothers who are the wives of men enlisted in the lower ranks of the Armed Forces and whose pay, it is assumed, would be insufficient to provide adequate and proper maternity service for their dependents. The Federal Government has undertaken to furnish what essentially is a supplement to the soldier's pay and a carefully studied act has been developed through the agency of the Children's Bureau by which a large sum of money was appropriated by Congress for this purpose. The provisions of the act have been accepted by most of the States in the Union although many of its administrative and other features leave much to be desired. However the medical profession has given its support and is wholeheartedly prepared to fulfill its functions. It recognizes, as do other interested agencies, that only the highest standards should prevail but it protests the perversion of the purposes of the Maternal Welfare Act by the amendment to the same appended by Congress at a last minute. As it stands the Bill approved by the President contains the following proviso relating to appropriations for the Department of Labor:

"Provided, that no part of any appropriation contained in this title shall be used to promulgate or carry out any instruction, order, or regulation relating to the care of obstetrical cases which discriminates between persons licensed under state law to practice obstetrics: Provided further, that the foregoing proviso shall not be so construed as to prevent any patient from having the services of any practitioner of her own choice, paid for out of this fund, so long as state laws are complied with."

And what does this mean? It means a broadening of the section relating to free choice of physicians as to permit so-called graduates

of diploma mills, including osteopaths, chiropractors, naturopaths, and all the other cults, and untrained and ignorant midwives, all without adequate scientific training in obstetrics, to furnish maternity care at government expense, provided "the state laws are complied with."

The high standards set up by the Children's Bureau in cooperation with its Board of Consultants are undermined by this amendment which, to their great credit, was vigorously opposed by several outstanding members of the Senate. A principal one among the arguments advanced in Congress during the debate on the measure was to the effect that the original, unamended bill constituted an "invasion of states rights," whatever that may mean in the face of other "invasions" in recent years. Such argument constitutes a mere political subterfuge, perhaps to satisfy the growing legion of cultists of all types who already have prevailed upon state legislatures to grant them certain, although often restricted, rights of practice.

A measure of this kind calls attention to one of the weaknesses inherent in political dictation of medical practice and should not be tolerated. Untrained and inadequately trained individuals undertaking the care of pregnant women and operating with the encouragement of the Government will constitute a menace to our prospective mothers and their children. It is quite needless to point out the resulting deaths and injuries which are sure to follow. Every physician with the welfare of his community at heart owes it to himself and his profession to convey to his congressional representative a vigorous protest as soon as possible.

The casualties of war, whether by death or invalidism, among our young married men in the ranks, emphasize the importance of giving proper care to their wives during childbirth. The mere provision of offering such care means little unless high standards are maintained. It is to be hoped that future sessions of Congress will be impressed sufficiently not to repeat the error they have committed in the passage of the undesirable amendment referred to. Immediate action is needed and in no way can this be accomplished more effectively than by concerted individual efforts on the part of those most definitely interested, namely, the members of the medical profession.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

A beautifully illustrated monograph on **The Diagnosis of Uterine Cancer by the Vaginal Smear** by Papanicolaou and Traut¹ is based on the recognition of individual cells or small groups of cells even in the pre-invasive stage. This method, now used for three years, was developed during the course of the study of thousands of vaginal smears at various ages and stages of the menstrual cycle. Even in the early stages of cancer, exfoliation occurs and these minute fragments are recoverable in the vaginal discharge.

The monograph first describes all phases of the smear in the normal cycle, amenorrhea, menopause, ectopic pregnancy and abortion. Next come the smears in carcinoma of the fundus and cervix. Colored plates of exceptional excellence illustrate the text.

The authors recommend diagnostic curettage for confirmation, a caution very necessary because of the great variations in smears, due to physiological phases as well as to possible complicating factors as pregnancy and inflammation. Much experience is needed to interpret the findings. It would have been of advantage to include the staining technique in detail in the text rather than giving a reference to its original publication in the literature.

R. T. FRANK.

Goodall presents a monograph entitled **A Study of Endometriosis**,² which includes Endosalpingiosis, Endocervicosis and Peritoneo-ovarian Sclerosis. The latter includes the syndrome described by Russell, the final stage of which results in a frozen pelvis. According to the author, a spontaneous arrest of endometriosis takes place in about sixty per cent of cases. Many will differ with the author as to the frequency of spontaneous regression. According to the author, endometriosis takes its primary origin always from the endometrium. In other words, he is a firm follower of Sampson's theory of implantation or transplantation. Certainly there will be many dissenters from the dictum "that endometriosis of whatever form is an expression of a vitiated endocrine function and consequent imperfect metabolism." So far nothing in the hormonal investigations, both blood and excretory, confirms this hypothesis. The description of the cases of "acute stromatous endometriosis with restricted malignant characters" as far as I can judge from Fig. 5 and 6, conforms to the disease I described under the term of "Fibromyosis": An Unclassified Plexiform Endolymphatic Proliferation of the Uterus, With Report of Three Cases (*American Journal of Cancer*, 1932, volume 16, page 1326). In my opinion, this was a condition of low malignancy which Robert Meyer, who studied the slides,

¹**Diagnosis on Uterine Cancer by the Vaginal Smear.** By George N. Papanicolaou, M.D., Ph.D., Department of Anatomy, Cornell University Medical College, and Herbert F. Traut, M.D., Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital. 47 pages. The Commonwealth Fund, New York, 1943.

²**A Study of Endometriosis, Endosalpingiosis, Endocervicosis, and Peritoneo-Ovarian Sclerosis. A Clinical and Pathological Study.** By James Robert Goodall, O.B.E., B.A., M.D., C.M., D.Sc., F.I.C.S.(Hon), F.R.C.O.G. Formerly Professor of Clinical Gynecology and Obstetrics, McGill University; Consulting Staff in Gynecology and Obstetrics, Royal Victoria, Montreal Maternity Hospital, etc. 13 illustrations in black and white and 17 subjects in full color on 6 plates. 140 pages. J. B. Lippincott Co., Philadelphia, 1943.

considered a sarcoma. Certainly such cases cannot with any degree of certainty be included among endometriosis.

That the endometriotic proliferations are directly influenced by the ovarian hormones is fully substantiated by the fact of regression after double oophorectomy or adequate radiotherapy to the ovaries, but this does not in any way make the author's belief acceptable "that quantitative vitiation in the nature of an excess of production of estrin is the factor in the genesis of endometriosis." There are too many other possibilities that must be taken into consideration. In spite of the fact that many of the hypotheses brought forward are not convincing, the monograph gives a very detailed and thorough study of endometriosis.

R. T. FRANK.

Gynecology With a Section on Female Urology by Wharton³ is more than a one thousand page, profusely illustrated textbook. The author stresses that gynecology is no longer a surgical art, but largely also medical and preventive; likewise that the distinction and differentiation between functional and organic disorders must be emphasized. The book covers every phase of gynecology as well as associated phases of urology in detailed fashion. His connection with Johns Hopkins since 1915 has made him aware of the responsibility of the teacher and the consequent necessity of distinguishing between personal opinion and established fact.

The numerous illustrations are of excellent quality. In the main, they are culled from sources based at Johns Hopkins, particularly from Cullen, Kelly, Kelly and Burnam, Novak and Young. On the whole, the text does not differ from well accepted and standard teaching. It is orderly, well arranged and sufficiently easy to grasp. The operative techniques are shown by numerous and detailed illustrations which make them useful even to the specialist. On the other hand, the chapter bibliographies are not representative and appear somewhat haphazard. One chapter, namely that on diseases of the vulva, was contributed by Laman A. Gray.

The reviewer considers the spectroscopic examination of the blood to determine ovulation as described by Samuels, not worthy to be included in any serious textbook. Clow's method for the treatment of dysmenorrhea does not, in the reviewer's opinion, deserve the endorsement which it receives. It would appear proper to include the Schatz and Gellhorn types of pessaries in a list of these useful instruments. I cannot agree that fertility is restored in about 35 per cent of women below the age of 40 by performing myomectomy. In my experience, myoma bearers, if anything, are among the fertile group.

The presentation on the whole is very readable. However, the shades of Achilles Rose must squirm at the phrase "If a woman with an outspoken endocrinology does conceive . . ." In the treatment of embolism, no mention of either hirudin therapy or of embolectomy has been included.

R. T. FRANK.

The fourth edition of Berkeley and Bonney's **A Textbook of Gynaecological Surgery**⁴ has appeared after an interval of six years. This large textbook covers the ground in a most thorough fashion. It includes not only the ordinary gynecological subjects but a detailed description of cesarean section, both abdominal

³**Gynecology With a Section on Female Urology.** By Lawrence R. Wharton, Ph.B., M.D., Associate in Gynecology, The Johns Hopkins Hospital; Consultant in Gynecology, The Union Memorial Hospital, Hospital for Women of Maryland, Sinal Hospital and Church Home and Infirmary. 444 illustrations. 1,006 pages. W. B. Saunders Company, Philadelphia and London, 1943.

⁴**A Textbook of Gynaecological Surgery.** By Sir Comyns Berkeley, M.A., M.C., M.D., Cantab., F.R.C.P. Lond., F.R.C.S. Eng., M.M.S.A. (Hon), F.R.C.O.G., and Victor Bonney, M.S., M.D., B.Sc. Lond., F.R.C.S. Eng., F.R.A.C.S., M.R.C.P. Lond. 4th Edition. With 574 Original Drawings by Victor Bonney and 17 Colour Plates. 912 pages. Cassell and Company, Ltd., London, New York, Toronto and Melbourne, 1942. Paul B. Hoeber, Inc., New York. (Rough Proof).

and vaginal. In addition, there is a complete chapter dealing with intestinal surgery. The volume has a very intimate and personal touch. The illustrations, which are excellent line drawings, were all made by Bonney himself.

Of particular interest are the statistics on carcinoma of the cervix. As is well known, Bonney has persisted in performing the Wertheim operation. In 500 cases, 5-year cures were obtained in 43 per cent; 10-year cures in 36 per cent. His personal operability rate is about 63 per cent of the patients seen. He regularly removes the obturator and hypogastric glands. On the other hand, the postoperative deaths in 1,192 cases following Wertheim operation were 16.1 per cent. Another operation in which Bonney is particularly interested is myomectomy, the description of which is extremely detailed and well illustrated. He employs clamps for temporary hemostases and performs extremely radical myomectomies with good final results. The description of Manchester prolapse operation (which he persists in calling the Fothergill), as well as his illustrations of this, show that it is not quite as anatomically performed as in America because the fasciae are neither sufficiently exposed nor sufficiently well included in the sutures. I note that he still unites the levator muscles in perineorrhaphies although most American operators have abandoned this type of repair.

The book can be warmly recommended because of its thoroughness and the large number of illustrations in the text (574). The reviewer is unable to discuss the 17 colored plates which were not included in the rough proof submitted for review.

R. T. FRANK.

Gynecologic Surgery by Goldberger⁵ is the first in a series, "Oxford Medical Outline Series." This series covers many branches of medicine and surgery. The book was written as a working guide to gynecologic surgery. It is interleaved in order that personal records can be appended.

This short, compact book covers the field of gynecological surgery in a minute fashion. In each instance the general anatomical considerations, the underlying pathology and the method of treatment are indicated. The main feature is a detailed abstract of practically every gynecological operation. The presentation is methodical, concise and clear. The student can readily follow the steps of the operation; the occasional operator can refresh himself in a few moments on the details of operative procedures.

R. T. FRANK.

Obstetrics: Embryology

The visualization of operative procedures has been fathered in recent years by extended use of the moving picture method. But no matter how carefully done, the impression is more or less momentary and fleeting.⁶ It has its value but this is a limited one. The rapidly succeeding flashes in the steps of an operative procedure afford little opportunity for close or careful study. There is an element of glamor in a motion picture demonstration, but there is not that satisfying experience which is afforded by unhurried examination of a well executed drawing.

The new work of Dr. Titus presents in satisfactory pictorial form the generally accepted obstetric operations together with a few others in closely allied fields. It is well done and there evidently was a close spirit of cooperation between author and artist. The pictures are to be commended for being simple and easily understood, no effort or labor was spent in "landscaping." In view of the size of the

⁵**Gynecologic Surgery.** By Morris A. Goldberger, M.D., F.A.C.S., Associate in Gynecology, Columbia University; Associate Gynecologist, Mount Sinai Hospital, N. Y. 164 pages. Oxford Medical Outline Series. Oxford University Press, New York, 1942.

⁶**Atlas of Obstetric Technic.** Paul Titus, M.D. Illustrations by E. M. Shackelford. St. Louis. C. V. Mosby Co., 1943.

printed page, many of the cuts might well have been made somewhat larger. The book constitutes a very practical addition to the list of American obstetric works for both practitioner and student and is deserving of wide attention.

GEORGE W. KOSMAK.

For thirty years DeLee's "*Principles and Practice of Obstetrics*"⁷ has been regarded as one of the outstanding textbooks on the subject. It is fortunate that through the work of Doctor Greenhill, who was long associated with Doctor DeLee, a new eighth edition is offered to medical students and practitioners. In the preface to this edition, Dr. Greenhill states that most of the changes and additions in the present volume had received Doctor DeLee's approval. The rearrangement of the material in the early part of the book makes for a more logical sequence of the material presented.

The new author's extensive knowledge of obstetric literature and his discriminatory ability in selecting the more important advances in obstetric sciences and practice has brought about in this volume the addition of recent worth while developments. There are many new sections in the text. A very conservative attitude is taken on the therapeutic value of certain hormones. The new ideas on erythroblastosis fetalis are discussed particularly with regard to transfusion accidents. The proper time to use vitamin K is brought out. The author has endeavored to evaluate the position of Water's extraperitoneal cesarean sections; he feels that sufficient time has not elapsed to determine the time and place of its choice.

Toxemias have been discussed on the basis of the classification proposed by the American Committee on Maternal Welfare. The importance of antenatal study and the necessity for prolonged follow-up has been stressed. There is an extended discussion of contracted pelvis and the classification and the work of Caldwell and his associates and Thoms has been included.

The sympathetic understanding of Doctor DeLee's teachings is apparent in the manner in which the new material has been included without effecting any changes in the principles laid down by the former author. The present revision will ensure the text's retaining its accepted place in obstetric literature.

PHILIP F. WILLIAMS.

Doctor Beck presents his *Obstetrical Practice* in a third revised edition⁸ in which he has incorporated such additions as have seemed suitable to keep the subject matter abreast of the times. It is of interest to note that since the second edition appeared, a Portuguese edition of the book has been prepared. The most marked change in this edition has been the subdivision of the section on operative obstetrics into six separate chapters. This may reflect the increasing tendency to induce labor at term as well as the increasing incidence of operative delivery and especially with regard to the interest of the child when premature labor is induced for various, particularly medical, complications.

In the section on cesarean section, there is an extended discussion, very well illustrated, of the extraperitoneal cesarean section proposed by Waters. The advan-

⁷*The Principles and Practice of Obstetrics.* By Joseph B. De Lee, A.M., M.D. Formerly Professor of Obstetrics and Gynecology, Emeritus, University of Chicago; Consultant in Obstetrics, Chicago Lying-in Hospital and Dispensary; Consultant in Obstetrics, Chicago Maternity Center, and J. P. Greenhill, B.S., M.D., Attending Obstetrician and Gynecologist, Michael Reese Hospital; Obstetrician and Gynecologist, Associate Staff Chicago Lying-in Hospital; Attending Gynecologist, Cook County Hospital; Professor of Gynecology, Cook County Graduate School of Medicine. With 1,074 illustrations on 841 figures, 209 of them in colors. 8th Edition, entirely reset. 1,101 pages. W. B. Saunders Company, Philadelphia, 1943.

⁸*Obstetrical Practice.* By Alfred C. Beck, M.D. Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Third Edition. More than 1,000 illustrations. 938 pages. Williams & Wilkins Company, Baltimore, 1942.

tages and disadvantages of three types of cesarean section, low cervical and extra-peritoneal and Porro, are discussed at length, and this discussion should be of benefit in the selection of the particular operation under varying circumstances. The illustrations in the section on cesarean section are partly colored which lends to their clear understanding. Doctor Beck has stressed the advantages of local anesthesia not only here, cesarean section technique, but in vaginal delivery. Under the discussion of anesthesia Doctor Beck mentions that caudal anesthesia destroys the pelvic floor reflex thus eliminating bearing down efforts and necessitating almost uniform forceps delivery.

While the presentation of obstetric principles and the multitude of well-executed illustrations have made this one of the best books for students, the present chapters on operative obstetrics in this edition add much to the value of the book for the practitioner who may be called upon to do obstetric surgery.

PHILIP F. WILLIAMS.

The Neuromuscular Maturation of the Human Infant,⁹ written by Myrtle B. McGraw and published by The Columbia University Press, New York, 1943, is, according to the author's preface, a volume which comprises a summation of a series of studies begun more than a decade ago. The conclusions drawn are based on a longitudinal study of the neuromuscular development of a group of children from infancy to early childhood.

The study of these infants has demonstrated a parallelism in the increased proficiency of their neuromuscular activity and the gradual maturation of the central nervous system. Dr. McGraw shows that much of the motor, often purposeless, activity of the newborn results from stimuli originating in the subcortical nuclei of the brain. As the child grows older and the cerebral cortical development progresses (maturation), the motor function becomes more mature, direct, and purposeful. She points out that the maturing cerebral cortex has an inhibitory control on stimuli arising in the subcortical areas, which finally results in a more mature neuromuscular function.

A few of the neuromotor activities of the infant are described in detail, such as the Moro or startle reflex, suspension grasp behavior, swimming, postural adjustment, crawling, and others. It is interesting that in each of these spheres of activity is demonstrated the change from early, less organized, subcortical activity to more mature, organized cortical control.

In a chapter, "Individual Development," she emphasizes that the rate of neuromuscular maturation is individualistic. Whereas it is limited by age and I.Q., it may not run parallel with these variables. In other words, each child more or less has his own rate of neuromuscular maturation, and the development of a particular activity will bear a constant relation to the rate of maturation in an average group. A similar maturation is demonstrated in early sensory development.

In a final chapter "Maturation and Learning," within a few pages Dr. McGraw boils down to pill size a potent concentrate of the educational values made apparent by her studies. Her suggestions regarding new pedagogical approach in infant and child training, based on her observations, must point the way in all of our future educational programs for young children, and in many ways must form a nucleus for a whole new school of thought along these lines. Much insight into her educational concept can be gained from one of her tabulated sayings: "Training in any particular activity before the neural mechanisms have reached a certain state of readiness is futile."

MITCHELL I. RUBIN.

⁹**The Neuromuscular Maturation of the Human Infant.** By Myrtle B. McGraw. 140 pages. Columbia University Press, New York, 1943.

The 1942 Year Book of Obstetrics and Gynecology¹⁰ is edited by J. P. Greenhill who has long been connected with this excellent review of the world's literature on these subjects. Dr. Greenhill has now assumed the editorship of both subjects. This volume is dedicated to Joseph B. DeLee, Editor for the Department of Obstetrics for this series from 1903 to 1941 inclusive. A brief history of Dr. DeLee's professional career is appended as a foreword.

The book maintains the high standard of the volumes of previous years. The development of medical literature on gynecologic-endocrinology is manifested by the inclusion in this volume of almost one hundred pages of abstracts on this subject. One misses in this volume the pithy, personal and often caustic editorial notes of Dr. DeLee.

PHILIP F. WILLIAMS.

Howard B. Adelmann, Professor of Histology and Embryology at Cornell University, has undertaken the difficult task of presenting the embryological treatise of Hieronymus Fabricius, by presenting a facsimile edition as well as a translation of *De Formatione Ovi et Pulli* and *De Formato Foetu*.¹¹ Of particular interest are the introductory chapters which show that Fabricius had studied comparative and human anatomy, embryology and surgery. One of his major achievements was that of discovering and describing the valves of the veins, in addition to the embryology of the egg of the chick.

Adelmann gives a detailed biography of Fabricius who obtained his degrees of M.D., and Ph.D. in 1559, at Padua, and in 1565, succeeded Fallopius. From then on, until he retired in 1613, he remained professor at Padua, including the title "supra ordinareus" in anatomy and surgery. Fabricius' fame extended throughout Europe. He had a large influx of students from Germany, Poland and France. Apparently, though he attracted students, he had continuous ructions and discords with them in spite of the fact that he was highly thought of and beloved. The main cause of the trouble was that he frequently failed to give adequate courses in anatomy. In 1584, he made dissections of a living pregnant ewe. In addition to his anatomical and physiological studies, he was a busy physician and surgeon, attending many famous personages and acquiring a large fortune. At his death, he left 200,000 ducats. Probably the best known pupil of Fabricius was William Harvey. His discovery of the circulation of the blood is said to have been founded on the description of the valves of the veins by Fabricius. The large and imposing volume published by the Cornell University Press, contains not only the life of Fabricius, but a sketch of embryology from antiquity to Fabricius: then an analysis of the embryological treatises of Fabricius. There follows a translation of Fabricius' "The Formation of the Egg and of the Chick" and that of "The Formed Fetus." Following this are facsimiles of these two classical works, very beautifully done and containing excellent reproductions of the plates which illustrated these works. In addition, there are full references. Altogether this makes a very complete presentation which should be of inestimable value to libraries and to all interested in the history of medicine, particularly the history of embryology and obstetrics.

R. T. FRANK.

¹⁰The 1942 Year Book of Obstetrics and Gynecology. Edited by J. P. Greenhill, B.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Loyola University Medical School, Chicago; Professor of Gynecology, Cook County Graduate School of Medicine; Attending Gynecologist, Cook County Hospital; Attending Obstetrician and Gynecologist, Michael Reese Hospital; Author of Office Gynecology and Obstetrics in General Practice; Co-author of the DeLee-Greenhill Principles and Practice of Obstetrics. 672 pages. The Year Book Publishers Inc., Chicago, 1943.

¹¹The Embryological Treatises of Hieronymus Fabricius of Aquapendente. The Formation of the Egg and of the Chick (*De Formatione Ovi et Pulli*). The Formed Fetus (*De Formato Foetu*). A Facsimile Edition, with an Introduction, a Translation, and a Commentary by Howard B. Adelmann, Professor of Histology and Embryology, Cornell University. 883 pages. Cornell University Press, Ithaca, New York, 1942.

Krafka's *Human Embryology*¹² is part of the Medical Students Series which appears under the editorship of Fred C. Zapffe. The volumes on bacteriology and medical biochemistry have already appeared. This series aims to give the basic foundation and to omit nonessentials in order that a student may possess a textbook which he has time to read in spite of the present huge and diverse curriculum, and one he can afford to buy.

Krafka has succeeded in supplying such a textbook of embryology. Because of our advance in knowledge, the material in this embryology is practically based on humans and no longer requires reference to less developed and more primitive forms. In spite of its limitations, the treatment of the subject is very detailed, and therefore can be referred to not only by the student, but by those interested in looking up various points in embryology or refreshing their knowledge of the subject. The simple line drawings which doubtless aid in keeping down the cost, are very satisfactory. The chapters on the embryology of the female and male genital tracts are excellently handled.

In describing hormonal regulators, the author uses such expressions as antituitrin S and progynon B, which are trade names, respectively, for chorionic gonadotropic, and estrogenic products. The same may be said of the use of antuitrin G. For a future edition, it might be well to remember that the accepted spelling of estrogens and androgens is not "estrogenes" and "androgenes." On the whole, the book can be highly recommended because of its clarity, detailed discussion, and compactness. The chapter bibliography is of value.

R. T. FRANK.

The articles contained in this memorial issue are dedicated by their authors to Dr. George L. Streeter, the well-known Director of the Department of Embryology from 1917 to 1940.¹³ It is a worthy tribute to an American scientist who has achieved the highest rank in this field, with its important bearing on medicine and particularly on obstetrics. The embryological collections of the Baltimore laboratory, developed so largely by Dr. Streeter, constitute one of the most important in the world and have been widely acclaimed. For their preparation and availability to students, gratitude and appreciation should be extended by all research workers.

The contents of the present volume include ten important articles devoted to a variety of topics on embryologic development which cannot be discussed in detail here but merit careful reading by those interested. Several of these deal with the human embryo in the earliest stages, one describing the presomite stage, by W. C. George, and another, very extended, by Streeter himself, of specimens in the 13 to 29 somite stages.

The book is beautifully printed and illustrated and worthy of the high praise which will be accorded undoubtedly by research workers.

GEORGE W. KOSMAK.

This volume constitutes a complete and satisfactory record of the valuable meeting held in St. Louis, April 6 to 10, 1942,¹⁴ under the sponsorship of the American Committee on Maternal Welfare. The Congress itself was an important and well-attended gathering whose proceedings may be regarded as a current reference work in the entire domain of obstetrics and gynecology, together with its related fields of activity. The varied contents are too extensive to be readily summarized and it is

¹²*Human Embryology*. By Joseph Krafka, Jr., M.D., Ph.D. Professor of Microscopic Anatomy, University of Georgia School of Medicine. With 222 illustrations. 395 pages. Medical Students Series. Paul B. Hoeber, Inc., New York, 1942.

¹³*Contributions to Embryology*. Volume XXX (Nos. 187-197). Published by the Carnegie Institute of Washington, Washington, D. C., 1942.

¹⁴*Transactions of the Second American Congress on Obstetrics and Gynecology*. Western Journal of Surgery Publishing Co., Portland, Oregon, 1943.

unfortunate that no index was prepared. The book is deserving of the appreciation of the medical profession and of those interested in the allied fields of hospital care and social service.

GEORGE W. KOSMAK.

Doctor Josephine H. Kenyon's valuable contribution to the lay literature on pediatrics, **Healthy Babies Are Happy Babies**,¹⁵ appears in a third edition, eleventh printing of the book in ten years. Such perennial popularity is sufficient recommendation of the value of the book to the young mother. Much new material has been added, particularly with regard to infant feeding, maternal nutrition, communicable diseases and other important phases of prenatal and child care. Probably one reason this book is so popular among parents lies in the fact that all the essential information relating to a certain age level may be found in one chapter. The discussion of prenatal care is excellent, as are also the remarks on the post-natal period. The final chapter on emergencies is brief and sensible in its discussion on the home accidents of infancy and childhood. A splendid book, to be recommended highly to young mothers.

PHILIP F. WILLIAMS.

Miscellaneous

Autonomic Regulations by Gellhorn¹⁶ is a most important contribution to all branches of medicine. It includes a large amount of the author's own work and should be of interest to every medical man because not only physiology but psychology and neuropsychiatry are included in the discussion.

The autonomic nervous system tends to preserve the internal environment of the body; the parasympathetic functions the local reflexes; the sympathetic, mass reflex reactions. There is an intimate connection between the autonomic and somatic nervous system, the latter adjusting the organism to the outside world. Not only are these systems affected by afferent and efferent impulses, but also by chemical alterations. The quantity of blood carried to the receptors of the sino-aortic area serves as a control. A marked difference between the effect of denervation upon the central nervous system and the autonomic exists. Structures enervated by the autonomic do not undergo degeneration or atrophy when denervation is produced.

The monograph does not lend itself to detailed review. The main chapters deal with adjustment reactions involving primarily the respiratory and circulatory systems; the autonomic-endocrine integration, the autonomic somatic integration, and finally, results and application of these physiological data. In covering this extensive ground, a certain amount of repetition is unavoidable. Fundamental reactions are ascribable to asphyxia, anoxia with retention of carbon dioxide, bleeding, hypoglycemia. Certain similarities of reaction are striking, for example, hypoglycemia and anoxia as well as emotional excitement diminish the oxidation rate of the brain, stimulate the sympathetico-adrenal system and reduce body temperature. The general similarity and the differences in the adjustment reactions in anoxia, CO₂ tension increase, bleeding, hypoglycemia, and emotional excitement are described in succeeding chapters. The homeostatic adjustment is maintained by the adrenalin inhibiting action of the hypothalamus and medulla. A discussion of the brain circulatory changes under experimental and natural conditions follows. An important portion is devoted to the autonomic endocrine integration. The rate of

¹⁵**Healthy Babies Are Happy Babies. A Complete Handbook for Modern Mothers.** By Josephine Hemenway Kenyon, M.D. Third Edition Completely Revised. 343 pages. An Atlantic Monthly Press Book. Little, Brown & Co., Boston, 1943.

¹⁶**Autonomic Regulations. Their Significance for Physiology, Psychology and Neuropsychiatry.** By Ernst Gellhorn, M.D., Ph.D., Professor of Physiology, College of Medicine, University of Illinois. With 80 illustrations and frontispiece. 373 pages. Interscience Publishers, Inc., New York, 1943.

secretion of various pituitary hormones, both anterior and posterior, are influenced by the hypothalamus, and as the hypothalamus has been proved to be the site of emotion, it is not surprising that the rate of secretion of these hormones can be influenced by emotional disturbances. (This will give a more sound basis to the clinical observation of amenorrhea as well as menorrhagia resulting from shock, the explanation of which has long puzzled gynecologists.)

Chapters are devoted to the convulsive states, to the subcortical site of emotions. The hypothalamus must be regarded as the center of autonomic and somatic integration of the motor expressions of emotion. The concluding chapters deal with the results and the application of these physiological discoveries, particularly the autonomic nervous system and neuropsychiatry. In schizophrenia there is a decreased reactivity of the sympathetico-adrenal system with relative predominance of the vago-insulin system. The effect of convulsive therapy appears due to a stimulation of both of these autonomic systems. Anyone who will carefully read and study this monograph will deepen his insight into every phase of medical practice.

R. T. FRANK.

Family Treasures, a popular guide to heredity by David D. Whitney, professor of zoology at the University of Nebraska¹⁷ fits in well with the Humanizing Science Books. I still remember reading with pleasure "About Ourselves" by Needham. This book, designed for the laity, brings out, particularly by many and striking photographs, the essential basis of heredity. One chapter is devoted to the Mendelian theory, but the greater part is a pictorial presentation of the normal traits which are hereditary. Anyone, both lay and professional, will be interested in this brief and striking presentation. The book contains a glossary and is well within the scope of educated lay persons.

R. T. FRANK.

This book, **Essentials of Industrial Health**, by Doctor C. O. Sappington,¹⁸ is timely in these days of war production, speeded up assembly lines and absenteeism.

The book is divided into three parts: The first: "Industrial Health Administration" discusses briefly the development of industrial health and the classification and training of physicians to man such services and the specific function to be expected of industrial physicians.

The second part covers "Industrial Hygiene and Toxicology." Measures to eliminate the health hazards in plants and to improve the personal hygiene of workers are described.

The third part "Industrial Medicine and Traumatic Surgery" discusses the classification of the worker for the physical and mental requirements of his job. After describing many types of industrial accidents and diseases, the book closes with a chapter on workmen's compensation and rehabilitation procedures.

There are many references throughout the book to the subject of women in industry. The section on the worker and his job very distinctly brings out the subjects of disabilities of women in industry, their limitations under certain exposure conditions and added precautions which should be taken when women are employed.

¹⁷**Family Treasures. A Study of the Inheritance of Normal Characteristics in Man.** By David D. Whitney, Ph.D., Professor of Zoology, University of Nebraska. 290 pages. The Jaques Cattell Press, Lancaster, Pa., 1942.

¹⁸**Essentials of Industrial Health.** By C. O. Sappington, M.D., Dr. P. H., Consulting Industrial Hygienist, President, Central States Society of Industrial Medicine and Surgery, Editor of "Industrial Medicine." 63 illustrations. 626 pages. J. B. Lippincott Company, Philadelphia, 1943.

On the subject of pregnant women in industry excellent general recommendations are made, and the laws of various states, prohibitory and regulatory, are stated. The book should have a wide appeal under our present conditions of expanded industrial production.

PHILIP F. WILLIAMS.

This book, *Essentials of Syphilology*,¹⁹ has been prepared by Doctor Rudolph H. Kampmeier to provide a brief text on syphilis for the practitioner of medicine. The five hundred pages offer a very fine exposition of syphilis as it may be met in general practice or public health. One is impressed with the stress laid on the problems of syphilis control, particularly with regard to the administrative measures and epidemiologic factors and general education principles. The concept of syphilis as a systemic disease has been emphasized. To this end many illustrative reports and comments are included in the text.

From the standpoint of the obstetrician, the three chapters on "Syphilis and Pregnancy," "Syphilis and Marriage" and "Congenital Syphilis," the latter chapter written by Doctor J. C. Peterson, handle this subject in a very comprehensive manner. The author has stressed the importance of syphilis in the pregnant woman as one of the large problems in preventive medicine. This should prove a very popular text.

PHILIP F. WILLIAMS.

Allergy by Urbach, with the collaboration of Gottlieb,²⁰ is a formidable volume of 1,073 pages. This textbook covers the entire subject of allergy, a rapidly growing branch of medicine from every aspect. The author states that the term, allergy, should be limited to "antigen-antibody reactions." The skin tests alone are useless in food, drug and gastrointestinal allergies. Neither the histamine nor the acetylcholine theories as the basis of allergic reactions are confirmed.

The field of sensitivities is amazingly large. Sensitivity to nonprotein substances such as diodrast, light, carbohydrates and lipoid is now well established. The subject covers particularly the upper and lower respiratory tracts, rhinopathies, gastrointestinal, skin, nervous system, the eye, female genital tract, pregnancy and allergies in infants. The enormous field covered does not lend itself to detailed review. In the treatment of allergies, the administration of antigen in subthreshold doses to gradually neutralize the antibodies without producing shock, appears to be the best method in most instances.

Naturally in covering this huge field, which is by no means stabilized, many debatable points arise, and which it will take many years to settle. The volume is copiously illustrated, is well gotten up, and contains an enormous fund of information. Over 2,000 footnotes are appended and these are made readily accessible by a good author's index. It does not appear warranted in the present state of this subject to criticize statements made by the author with which we may individually disagree. The volume should be regarded not only as an excellent reference book, but because of the clearness and simplicity of presentation, it will prove of real use to those who are not specializing in this branch of medicine.

R. T. FRANK.

¹⁹*Essentials of Syphilology*. By Rudolph H. Kampmeier, A.B., M.D. Associate Professor of Medicine, Vanderbilt University School of Medicine; in Charge of Syphilis Clinic and Visiting Physician to Vanderbilt University Hospital. With Chapters by Alvin E. Keller, M.D., and J. Cyril Peterson, M.D. 57 illustrations. 518 pages. J. B. Lippincott Company, Philadelphia, 1943.

²⁰*Allergy*. By Erich Urbach, M.D., Chief of Allergy Service Jewish Hospital, Philadelphia, etc., with the collaboration of Philip M. Gottlieb, M.D., Associate on Allergy Service, Jewish Hospital, Philadelphia, etc. 1,073 pages. Grune & Stratton, New York, 1943.

The Sex Hormones,²¹ edited by F. C. Koch and Philip E. Smith, and preceded by a foreword by Frank R. Lillie, was one of a number of symposia presented as part of the fiftieth anniversary celebration of the University of Chicago on September 22 to 29, 1941. The monograph contains eight articles divided into two groups, the first, the sex hormones, their actions and metabolism; the second, dealing with the hormonal factors in the inversion of sex.

Moore describes the comparative biology of the testicular and ovarian hormones; Kenyon, their comparative metabolic influences. Doisy deals with the metabolism of estrogens; Koch with that of androgens. The latter paper includes clinical data.

Danforth discusses sex inversion as noted in the plumage of birds; Humphrey, sex inversion in the amphibia. Greene describes the effect of hormonal factors on embryonic sexual factors in the rat, and Burns, Jr., those noted in the opossum.

This symposium is short, clear and authoritative in dealing with these special fields of endocrinology.

R. T. FRANK.

A Family of Thirty Million by Louis I. Dublin, Ph.D.,²² is the story of the Metropolitan Life Insurance Company. This volume shows the important position of life insurance in every phase of life, including economic security, welfare of both its insured and its employees, and the importance which a well-conducted medical service plays, both from an actuarial and a social point of view. Chapters 20 and 21, which likewise appear in pamphlet form, cover the work done by this modern insurance company in welfare, and in conserving health and longevity.

R. T. FRANK.

Diseases of the Gastrointestinal Tract by Winkelstein²³ appears in the Oxford Medical Outline Series, previously mentioned in this review. This epitome gives a very detailed and compact presentation of all the gastrointestinal diseases, detailing the symptoms, tests, diagnosis, medical and operative methods of treatment. It will be found useful for quick review, as well as for details of treatment.

R. T. FRANK.

²¹**Biological Symposia.** A Series of Volumes Devoted to Current Symposia in the Field of Biology. Edited by Jaques Cattell, Editor of the American Naturalist and American Men of Science. Volume IX. **Sex Hormones.** Edited by F. C. Koch, Frank P. Hixon, Distinguished Service Professor and Chairman of the Department of Biochemistry of the University of Chicago and Philip E. Smith, Professor of Anatomy College of Physicians and Surgeons, Columbia University. 146 pages. The Jaques Cattell Press, Lancaster, Pennsylvania, 1942.

²²**A Family of Thirty Million.** The Story of the Metropolitan Life Insurance Company. By Louis I. Dublin, Ph.D., Third Vice-President and Statistician. 496 pages. Metropolitan Life Insurance Company, New York, 1943.

²³**Diseases of the Gastrointestinal Tract.** By Asher Winkelstein, M.D., B.S., Associate in Medicine and Physician in Charge of the Gastro-Intestinal Clinic, The Mount Sinai Hospital, New York City; Associate in Medicine (Gastro-Enterology), Post Graduate School of Medicine, Columbia University, New York City. 195 pages. Oxford Medical Outline Series. Oxford University Press, New York. 1942.

Department of Reviews and Abstracts

Selected Abstracts

Gynecology

Rubenstein, Boris B.: Premenstrual Headache Relieved by Estrogen Therapy, *J. Clin. Endocrinol.* 2: 700, 1942.

Detailed case histories are reviewed of six women suffering severe incapacitating premenstrual headaches which were relieved by estradiol dipropionate. Points of similarity, in addition to headache, among the women were: childbearing age; nervous, high-strung, active temperaments; and vaginal smears, interpreted by the author's method, indicating lowered premenstrual gonad hormone elaboration.

All were promptly relieved by administering estradiol dipropionate 1 mg., intramuscularly, generally in the early part of the premenstrual week, although timing and dosage seemed to require individual adjustment.

CLAUDE J. EHRENBERG.

Menstruation

Sturgis, Somers H., and Meigs, Joe V.: The Use of Estradiol Dipropionate in the Treatment of Essential Dysmenorrhea, *Surg., Gynec. & Obst.* 75: 87, 1942.

The cramps of essential dysmenorrhea can be prevented with estrogen, provided adequate dosage is given early enough in the cycle. The results in thirty-three patients treated with estradiol dipropionate are reported. The period of treatment covers 130 menses, 88 per cent of which were completely painless. Equally effective results are said to be obtained with estradiol benzoate or stilbestrol. Evidence is presented to show that such estrogenic therapy suppresses ovulation and thus painless cycles are produced.

J. M. HELLMAN.

Dysmenorrhea

Boynton, Ruth E., and Winther, Nora: The Treatment of Primary Dysmenorrhea With Estriol Glucuronide, *J. A. M. A.* 119: 122, 1942.

A study of one hundred girls with dysmenorrhea is presented. Fifty girls were given estriol glucuronide extracted from human placentas, and fifty were given a placebo. These girls were all college students ranging from 17 to 25 years of age. Each of the girls were given six tablets daily for ten days before each calculated menstrual period. The patients were treated for at least three months. Twelve per cent of the group receiving estriol glucuronide and 8 per cent of the group receiving placebos reported complete relief from dysmenorrhea for a period of 9 to 12 months. Thirty-eight per cent of those receiving estriol glucuronide and 58 per cent of those receiving placebos, obtained no relief whatsoever.

WILLIAM BERMAN.

Hansen-Pruss, O. C., and Raymond, Ruth: Influence of the Menstrual Cycle on the Titer of Circulating Allergens, *J. Clin. Endocrinol.* 3: 81, 1943.

In order to study experimentally the clinical observation "that the menstrual cycle influences the occurrence and severity of allergic phenomena," the authors employed the Prausnitz-Küstner technique of passive sensitization of skin sites. Passive transfer tests were made on five nonallergic males from four young females allergic to short ragweed at arbitrarily chosen times during the menstrual cycle. The results of the experiment indicate that the serum of allergic women contains the highest allergin titer on the last day of menstruation, and the converse in serum obtained ten days before the onset of menstruation. It is suggested that the relative dehydration of the period of estrogenic deprivation may be the cause of the phenomenon.

CLAUDE J. EHRENBURG.

Miscellaneous

Hoffman, Martin H.: Studies in the Metabolism of Progesterone, *Canad. M. A. J.* 47: 424, 1942.

In experiments upon the rabbit, it was demonstrated that progesterone is converted into pregnanediol and excreted as the glucuronide in both the male and female. The uterus and the testes are not essential for this conversion. Pregnanediol is excreted in the feces of rabbits given progesterone orally, but not if the drug is administered parenterally.

CARL P. HUBER.

Hall, Beatrice: Some Social Considerations in the Provision of Maternity Care at Public Expense, *Child* 6: 66, 1941.

A very comprehensive review on certain social and medical aspects of maternity care is presented. In introducing the subject she says, "the improvement that is taking place today in maternal and child health may be regarded as a culmination of a fundamental concern on the part of citizens, which has actively expressed itself for many years in a variety of programs supported through public and private funds. It may also be regarded as one manifestation of increased awareness on the part of the people generally of the influence of social and economic conditions upon the health of mothers and children, and the development of greater skill in cooperative effort, making possible a fuller utilization of all community resources in meeting the total problems of individuals."

It is axiomatic that the primary medical and social needs of mothers and children can be met only through cooperative work with families on the part of physicians, dentists, nurses, nutritionists, health educators, and social workers, of health agencies, both public and private, and of professional organizations and citizens' groups. The maternal and child-health programs of the U. S. Children's Bureau, under the Social Security Act, endeavors to work in cooperation with Federal, State and local agencies, and these in turn with other participating organizations. Specifically, in 1935 and 1936, a study of maternity care in six counties of New York State was undertaken by the Children's Bureau in cooperation with all agencies concerned. These agencies were varied in different counties, but in the final analysis the results were equally good. In some counties better "teamwork" was more noticeably good than in others. For example, in certain communities the welfare officers were not convinced of the importance of prenatal care, and therefore did not encourage women to register early in their pregnancies. In spite of this, the public health nurses were able to obtain early registration and good results obtained. Extension of clinics is

a good way of increasing early registration in any community. However, clinics are not practical in sparsely populated areas; consequently, in such communities, arrangements should be made with private physicians to give this service.

This demonstration proves beyond doubt, the feasibility of a cooperative plan including federal, state and local agencies in providing good maternity care at public expense.

HARVEY S. MATTHEWS.

van der Horst, C. J., and Gillman, Joseph: *A Critical Analysis of the Early Gravid and Premenstrual Phenomena in the Uterus of Elephantulus, Macaca and the Human Female*, South African J. M. Sc. 7: 134, 1942.

The authors interpret their observations on the uterus of the elephant shrew to mean that events in the endometrium are quite different, after the ova reach the uterus, according to whether the eggs are fertilized or not. If unfertilized, certain peculiar premenstrual changes occur; if fertilized, pregnancy changes take place. For histologic details, the original paper must be consulted. The point is, that in this species, it seems that premenstrual changes are not the same thing as the progravid changes. This is, of course, contrary to the current hypothesis of the menstrual cycle in man and the monkey, which supposes that menstruation is the breakdown of a progravid endometrium in case an embryo does not arrive. By analogy with their interpretation of the situation in *Elephantulus*, they think the endometrium of pregnancy in the monkey and human should begin to differ from that of menstruation as early as the sixth day after ovulation. Taking Wislocki and Streeter's descriptions of the monkey endometrium in early pregnancy, which were not intended to apply to the present question, they read them (erroneously, in the reviewer's opinion) in such a way as to support their own thought that premenstrual growth is not initiated in preparation for the reception of a fertilized ovum. It should be added that their views ignore a large body of experimental evidence; and that, moreover, the case of the elephant shrew, which is of course exceedingly interesting, to be clearly understood requires experimental analysis which is not possible at present because of difficulties in rearing the animals.

GEORGE W. CORNER.

van der Horst, C. J., and Gillman, Joseph: *The Spontaneous Development of Deciduomata in Elephantulus*, South African J. M. Sc. 7: 127, 1942.

In an elephant shrew, a tumor was observed in the uterine cavity which resembled in its structure the endometrium of early pregnancy and was interpreted as a deciduoma. In another animal, the endometrium of one horn of the uterus was in a condition resembling that of normal pregnancy about the time of implantation, although no embryo was present. To explain the occurrence of these conditions without any detectable stimulus, the authors cite two cases in which early embryos were degenerating about the time of implantation. They suppose that in each of the two abnormal cases an embryo had been present and initiated the changes, which went on after the disappearance of the embryo.

GEORGE W. CORNER.

van der Horst, C. J., and Gillman, Joseph: *Preimplantation Abortion in Elephantulus*, South African J. M. Sc. 7: 120, 1942.

The elephant shrew, a small South African insectivore, exhibits certain special phenomena of reproductive physiology. A considerable time elapses between the arrival of the embryo at the implantation site and actual implantation. The presence of the embryo at the implantation site excites a series of reactions in

the uterus. These are (1) edema of the endometrium; (2) formation of an embryo chamber; (3) swelling of the glands; (4) condensation of the stroma around the embryo chamber, leading to development of the decidua compacta. These reactions are evoked by the embryo seriatim and independently of each other, except that reactions (3) and (4) start simultaneously. At one time or another while the embryo is lying in the uterus unimplanted, it may die or be extruded from the special embryo chamber into the main uterine lumen. When such a preimplantation degeneration or "abortion" occurs, whichever of the above reactions may have begun, go on unchecked by subsequent reactions which would have happened if the embryo were alive. According to the time of death of the embryo, the result may be a very intense edema, an abnormally large embryo chamber, or a decidual reaction of pathologic character.

GEORGE W. CORNER.

Nelson, Edward W., Jones, J. R., and Collins, Conrad G.: *Pelvic Thrombophlebitis—A Study of the Etiologic Factors From a Statistical Standpoint*, New Orleans M. and S. J. 95: 375, 1943.

A group of forty-one cases of pelvic thrombophlebitis proved at autopsy or at the time of operation are reported. The gravity of this disease is emphasized and the etiologic factors contributing to its development are analyzed. Delivery, abortion, operation and irradiation are the most frequent precursors. Repeated aerobic and anaerobic blood cultures are necessary to establish the etiology. *Staphylococcus aureus* and nonhemolytic streptococcus were the most frequent offenders. The uterine veins, iliac veins, ovarian veins and inferior vena cava were involved in the order named. Pulmonary infarction is extremely common, and frequent x-ray of the chest in patients running a septic course with no clinical signs of pelvic thrombophlebitis will often establish the diagnosis when pelvic examination demonstrates no pathology. Early treatment will reduce the 50 per cent mortality associated with this disease and ligation of the inferior vena cava is recommended as the treatment of choice.

WILLIAM BICKERS.

Ryan, John D., Bauman, Eli, Mulholland, John H.: *The Blood Concentration and Excretion of Sulfadiazine*, J. A. M. A. 119: 484, 1942.

The authors describe the findings of blood and urinary concentrations of sulfadiazine when placed in the peritoneal cavity. The concentration of sulfadiazine in the blood following the intraperitoneal administration of the drug rises fairly rapidly and remains elevated for a considerable period of time depending upon the amount of the drug administered. With ten, twenty and twenty-five gram doses the effective blood levels persist for 48, 72, and 96 hours respectively. The drug need not, therefore, be administered by any other route for the first 2 to 4 days. The powder is readily absorbed from the peritoneum. Its absorption is somewhat slower than that of sulfanilamide, and, therefore, the authors feel it is better than local intraperitoneal implantation. There were no postoperative complications and no toxic manifestations were observed in any of the cases studied.

WILLIAM BERMAN.

Ivy, A. C., Greengard, H., Stein, I. F., Jr., Grodins, F. S., and Dutton, D. F.: *The Effect of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage*, Surg., Gynec. & Obst. 76: 85, 1943.

The authors studied the use of various blood substitutes in the case of severe hemorrhage in dogs. The control group consisted of fifty animals losing from 45 to 70 per cent of the blood volume. The mortality was 84 per cent.

When the loss was replaced by normal saline, the mortality was reduced to 58 per cent. Pooled serum proved to be somewhat better, further reducing the mortality to 26 per cent. The use of citrated blood or plasma, was not so satisfactory because the amount of citrate in so large a volume of plasma or blood, proved to be toxic. Heparinized plasma was the most satisfactory substance employed reducing the mortality to only 6 per cent. Gelatins, gum acacia, and peetin in large amounts were unsatisfactory because of the resulting pseudo-agglutination.

L. M. HELLMAN.

Davis, Harry A., and McNeely, George R.: *The Probability of Obtaining Potentially Dangerous Pools of Human Serum or Plasma*, Science 96: 468, 1942.

In a purely theoretical discussion on probabilities of obtaining pools of potentially dangerous plasma, the authors draw attention to a possibility that has hitherto been discounted. That this is a real danger, however, is evident from the near fatality reported by Polayes and Squillace, and from an unreported death occurring from plasma transfusion on the reviewers' service. Theoretically, pools of 9 to 14 plasmas should contain sufficient antagonistic iso-agglutinins to inactivate each other. By the use of simple mathematics it is possible to compute the possible predominance of one blood group in a pool, and thus a failure of the iso-agglutinins to become inactivated. The authors state that for pools of 16, the probability is 0.02 (i.e., odds of 1:50); for pools of 8, 0.14 (odds of 1:7); and for pools of 4, 0.44 (odds of 1:2.3). Tentatively a word of caution is given against the pooling of unknown blood groups. The danger would seem especially great in small pools.

L. M. HELLMAN.

Fox, Chas. L., Jr.: *Sodium Salts of the Sulfonamide Compounds*, Arch. Surg. 45: 754, 1942.

In experimental work on dogs, the author has found that the more soluble sodium salts of sulfapyridine, sulfathiazole and especially sulfadiazine are tolerated by the tissues with little or no reaction and no important effects on the pH of blood or tissue fluids. The powder forms a soft paste with the tissue fluids and the wound heals normally with no sign of caustic irritation. The advantage of the local use of the powder is in the immediate attainment of a high local concentration of the drug which is sustained for 24 to 48 hours while the drug is continuously and completely transferred into the general circulation. To those who have felt that sulfanilamide powder was the answer to local chemotherapy, the use of sodium sulfadiazine with success in humans now opens the way to the use of this more potent antibacterial drug (weight for weight). The urine alkalinity should be maintained to favor safe renal excretion of the drug.

ROBERT J. WEISSMAN.

Koster, H., and Kasman, L. P.: *Relation of Serum Protein to Well Healed and to Disrupted Wounds*, Arch. Surg. 45: 776, 1942.

Koster and Kasman, in animal experiments on the relation of hypoproteinemia to wound disruption, and in a study of serum protein in 1,358 consecutive hospital admissions, were able to compare forty cases of normal wound healing with forty cases of wound disruption and found low serum protein in the disrupting series, compared with the average serum protein in the normal cases. This, however, does not explain wound disruption in the presence of relatively high serum protein, or normal healing in the presence of low serum protein. The authors conclude that hypoproteinemia per se is not sufficient cause of the dis-

ruption, but may be considered a concomitant of the general status of malnutrition which obtains in these cases, and which may be said to favor disruption.

ROBERT J. WEISSMAN.

Dunayevich, Bernardo: Contribution to the Study of Permanent Dilatation of the Pelvis Following Symphysiotomy, *An. Inst. de Mat. y Asist. Soc.* 2: 38, 1940.

Bernardo Dunayevich presents a series of ten new clinical and roentgen observations made on women who had had symphysiotomies. Some of them were followed for many years after the operation. The author concludes that the separation of the pubic ligaments is permanent in all cases, and that the relative pelvic stenosis may be considered anatomically cured after the operation of partial symphysiotomy performed according to Zarate's technique.

J. P. GREENHILL.

Fuerstner, Paul G.: Further Experiences With Diethylstilbestrol, *West. J. Surg.* 50: 530, 1942.

Fuerstner reports his experience in the treatment of one hundred twenty-four menopausal patients. Of this group, one hundred eight have been followed sufficiently long to draw conclusions, seventy-two had menopausal symptoms alone while, nine had vaginitis, pruritus, or kraurosis associated with the vasomotor symptoms and twenty-seven in the older group had the local symptoms alone. The patients were treated with diethylstilbestrol and diethylstilbestrol dipropionate in the form of tablets, injection, or suppository. Dosage and method of administration must be individualized, usually the patient was given 1 mg. daily until her vasomotor symptoms were controlled and then the dose was gradually reduced. The gradual reduction of dosage is important to prevent withdrawal bleeding and the recurrence of symptoms after medication is stopped. The best yardstick for dosage is the patient's response to treatment. Surgical or radiologic castration requires larger doses than physiologic menopause. Often medication may be given every other day especially when the longer action dipropionate is used. The author reports recurrence of symptoms in 22.2 per cent of his series, complete relief of symptoms in 80.2 per cent of his menopausal cases. Cases of involutional melancholia or schizophrenia were not helped, but the milder forms of depressions improved. Local therapy in the form of suppository in the cases of vaginitis and pruritus was warmly approved. The sublingual route of administration using diethylstilbestrol in propylene glycol, 0.5 mg. to each drop, was used in a group of patients and the results were very satisfactory. Toxicity of stilbestrol is reviewed and the author states that it is most often seen in the woman with a hypersensitive neurovegetative system. A sensitive autonomic system is thought to be the important factor in the group of fifteen patients who suffered with nausea. The administration of belladonna alkaloids and ergotamine tartarate (Beller-gal Tablets) to depress the autonomic nervous system was found to reduce the nausea in the hypersensitive patients. Reference is made to some recent experimental work which shows that the estrogens favor glycogen deposit in the liver.

WILLIAM BICKERS.

Martin, W. Coda: Preliminary Report on the Relation of Vitamin C Deficiency to Varicose Veins, *West. J. Surg.* 50: 508, 1942.

It is thought that varicose veins are the result of a defective venous wall, in some cases congenital, but in many perhaps the weakness results from vitamin C deficiency. This vitamin is apparently essential for the normal embryologic development of connective tissue. In its absence the intercellular cement substance is defective, this is most important in normal connective and endothelial tissue.

The absence of this substance results in structural weakness of the vessel walls. It is pointed out that this fragility of the walls forms the basis for the capillary fragility test, and since the fragility is presumed to result from vitamin C deficiency, the author uses this test as an index to the patient's vitamin C reserve. It is emphasized that the dilatation of the veins and the valvular insufficiency seen in varicose veins may actually precede the reversal of the venous flow rather than follow it.

Twenty-five cases of varicosities in pregnancy were studied; of this group 76 per cent showed evidence of vitamin C deficiency as determined by the fragility test. Ascorbic acid blood levels were not done because at the time of this study laboratory facilities were not available. In contrast a group of normal pregnant controls without varicosities showed that 60 per cent had normal vitamin C intake and the other 40 per cent showed only very moderate deficiency. The author concludes that deficiency of the C vitamin causes intracellular weakness in the vessel wall which predisposes to varicosities. Increased intra-abdominal pressures may be a contributing factor.

WILLIAM BICKERS.

Newborn

Harris, T. N.: Treatment of Impetigo Contagiosa With a New Preparation of Sulfathiazole, *J. A. M. A.* 121: 403, 1943.

The author reviews the older and well established methods of treatment of this very common disease. He mentions the oral and local treatments of the disease with various drugs and reviews the time taken in the establishment of a cure. The new method is based on a physical principle developed by Chambers. This new form of sulfonamide yields a stable suspension of fine crystals. It resembles magnesia magma in physical appearance, and remains stable in pure water for many months. When allowed to dry, the suspension does not cake, but becomes a fine friable powder. This new form of sulfonamide has been called "microcrystalline." A twenty per cent suspension of this was used. A drop or two of this suspension is applied on a piece of gauze. This concentrates the sulfonamide crystals on the surface of the dressing. The area is first washed with soap and water. On removal of the dressing 24 hours later, the lesion was found to be healed. The microcrystalline drug maintains the separation of the crystals, assuring a much greater surface for solution into local tissue fluids, and a continued distribution over the lesions. The actual time of treatment is considerably reduced. Sulfathiazole was used in these studies because of its availability and its effectiveness on both streptococci and staphylococci. Microcrystals of other sulfonamide compounds have been produced and would presumably be as effective against susceptible bacteria.

WILLIAM BERMAN.

Barcroft, Sir Joseph: The Onset of Respiration at Birth, *Lancet* 2: 117, 1942.

In a very stimulating essay, the author describes the development of respiratory movements as they appear in the fetus of the ewe at varying periods of development and discusses the probable mechanism of the onset of respiration.

The development of movement generally and respiratory movements in particular may be divided into four stages which represent a gradual progression of activity.

Stage 1.—Spasm. This appears on the thirty-fourth or thirty-fifth day, and is a single spasmodic movement of the head and neck elicited by tapping the fetus sharply between the eye and mouth in an area corresponding to the region supplied by the maxillary branch of the fifth cranial nerve. As each day passes this spasm expands both in the muscles involved and in the area which responds to stimulation. By the thirty-eighth day, the diaphragm may be involved.

Stage 2.—Rhythm. By the fortieth day, the response is a series of spasms which increase in frequency and duration. During this time the intercostal muscles begin to play a part.

Stage 3.—Segregation. By the forty-fifth day, the initial response to stimulation is a general movement of the body followed by a continued respiratory rhythm, so that this phase of the movement becomes independent. By fifty days' movement can be elicited by stimulating nearly any part of the body.

Stage 4.—Inhibition. By the sixtieth day, the fetus has become inert. Very slight response follows stimulation. It remains normally quiescent until birth. The stage is set for the onset of respiration although only half of the period of gestation has elapsed.

The occlusion of the umbilical cord releases the inhibition and rhythmic respiratory movements start. Similarly if the cord is occluded during stage 3, the fetus reverts to stage 2 and in a like manner from stage 2 to 1, and from 1 to complete cessation of movement. By transection of the central nervous system the author concludes that stage 1 can be reproduced by section just above the nucleus of the twelfth nerve, stage 2 just below the pons, stage 3 just above the pons, and stage 4 just above the posterior corpora quadrigemina.

Respiratory movements from the sixtieth day on depend on a balance between inhibition and stimulation. In utero, inhibition is predominant. At birth two things happen. First, inhibition is depressed by asphyxia, and secondly, the brain is bombarded with volleys of sensation which raise the general sensitivity. The respiratory patterns which result are as follows: (1) The simple spasm or gasp; (2) the spasm or gasp involving the respiratory muscles outlasted by a respiratory rhythm of shallower respirations; (3) rhythms of shallow respirations which come and go, possibly not preceded by any obvious spasm; (4) the establishment of almost continuous respiration of a normal character. Which appeared would depend on the stringency of the conditions to which the fetus was subjected. The first would be that in which sensation was at its minimum and asphyxia at its maximum, the last at which sensation was at its maximum and asphyxia at its minimum. These are, what on a basis of observations in the sheep, we might expect to find in the child at birth.

CARL P. HUBER.

Barnes, Allan C., and Wilson, J. Robert: *Care of the Newborn Premature Infant*, J. A. M. A. 119: 545, 1942.

Babies (premature) are immediately placed in Trendelenburg position, the throat cleared of mucus, placed in a warm premature jacket, and given one hundred per cent oxygen inhalations. The child is handled as little as possible. Babies are not weighed and bathed routinely. Axillary temperatures are taken one to two hours apart until the infants temperature is stabilized. Infants weighing less than 1,800 Gm. are given 100 per cent oxygen to decrease the respiratory effort. Occasionally a mixture of 95 per cent oxygen and 5 per cent carbon dioxide is used to stimulate respiration. No feeding is given for the first 12 to 24 hours. For the first feeding day, 5 per cent dextrose is given and then a weak evaporated milk formula, or breast milk if available. The infant is not removed from the crib for feeding until it weighs at least 2,200 Gm. Isotonic fluids may be given subcutaneously. After the first few days of life, elixir of thiamine, one drop daily, increased until eight drops are given daily. A daily dose of ten drops of an iron solution may be given. This can be followed by vitamin D and orange juice. Protein milk may be added to the formula later. An attempt is made to increase the caloric intake from 75 to 100 calories per pound of body weight. This regime resulted in a survival rate of 90.5 per cent of all viable infants whose weight was between 1,000 and 2,499 Gm.

WILLIAM BERMAN.

Yerushalmy, J.: Maternal and Infant Mortality in the United States, Child 7: 110, 1943.

Throughout the United States, extraordinary progress has been made during the past few years in saving the lives of mothers and babies. The 1941 figures for maternal and infant mortality reveal new all-time low records. Available 1942 figures indicate a continued downward trend. This record is all the more commendable when it is realized that 1941 witnessed the rapidly expanding national defense program, which imposed an unusually heavy burden on the housing, sanitary, hospital, and medical facilities of practically every community throughout the country.

The reduction in maternal mortality rates in 1941 over 1940 was 16 per cent, which is the equivalent of saving 1,500 mothers. Compared to the figures for 1931, it meant the saving of 9,000 mothers' lives.

The infant mortality rates for 1941, although not so striking, continued their downward trend to reach an all-time low. The birth rate reached 18.9 for 1941, whereas in 1933, it had reached an all-time low of 16.6 per 1,000 population. Hospital births reached their highest point in 1941, 60 per cent. Furthermore, 91 per cent or 2,297,705 births were attended by physicians, an all-time high, while 215,722 or 9 per cent were attended by midwives or other nonmedical neighbors.

Notwithstanding the remarkable 1941 gains in our maternal and infant mortality rates, the loss of life associated with childbirth and early infancy is still too high. Look at the figures—197,038 lives were lost through maternal mortality, stillbirths, and infant mortality in 1941.

An extensive statistical summary, with many tables, is given; all of which has been compiled from the most recent reports from the Division of Vital Statistics of the Bureau of the Census, Washington.

HARVEY B. MATTHEWS.

MacLean, John T.: Hemorrhagic Infarct of the Testicle in the Newborn, Surg., Gynec. & Obst. 76: 319, 1943.

Two cases of hemorrhagic infarction of the testicle in newborn infants are reported. In both instances, delivery and labor were normal and terminated spontaneously. The diagnosis was made at birth by the presence of a mass in the scrotum and edema and discoloration of the sac. Orchidectomy was performed in each case, and the diagnosis confirmed by gross and microscopic section. The condition must be differentiated from hernia, hydrocele, epididymitis and testicular tumor.

F. M. HELLMAN.

Lund, Curtis J.: Fetal Distress During Labor, Illinois M. J. 83: 96, 1943.

Lund points out the great importance of "oxygen want" in causing death and disability of the fetus.

The types of anoxia usually recognized are: (1) Anoxia—a deficiency oxygen saturation of the blood. (2) Anemia—a diminished oxygen carrying capacity of the blood. (3) Stagnant—an impaired or slowed circulation of blood. (4) Histotoxic-impaired cell metabolism so that available oxygen cannot be utilized.

The author's conclusions: Primary oxygen want is responsible for many fetal deaths. In addition anoxia may produce temporary or permanent damage to vital centers within the central nervous system. Temporary anoxic depression of the respiratory center is a factor in the production of neonatal asphyxia.

Fetal asphyxia is best recognized by a sudden or gradual slowing of the fetal heart rate. This sign is of greater diagnostic value than are those of excessive fetal movements or the presence of meconium.

In many instances, the anoxia is reversible and can be successfully treated by administration of oxygen to the mother. An improvement of fetal heart rate indicates successful therapy. Other therapeutic measures sometimes indicated include deep anesthesia, administration of atropine and "flushing" the mother with oxygen at the moment of birth.

F. L. ADAIR.

Schachter, M.: Congenital Pseudo-Nevus of the Newborn of Fruhinsholz and Hartemann, *Monatschr. f. Geburtsh. Gynäk.* 113: 317, 1942.

The author describes a rare condition in newborn infants which consists of a pseudo-nevus at the root of the nose. The nevus usually disappears spontaneously. The author reports the first case observed in double ovum twins. From this case he assumes that the nevus originates in the period after fertilization.

J. P. GREENHILL.

Kitzmler, J. L., and Mitchell, W. B.: Vagitus Uterinus, *West. J. Surg.* 50: 621, 1942.

The cry of an infant in utero was recorded as early as 1730, numerous reports having since appeared in the literature. Three conditions must be present:

1. The membranes must be ruptured.
2. Some manipulative operation to stimulate the fetus.
3. Air must enter the uterus.

A case is reported in which the unborn fetus was heard crying during the process of breech extraction.

WILLIAM BICKERS.

Perlman, H. Harris, Dannenberg, Arthur M., and Sokoloff, Nathan: The Excretion of Nicotine in Breast Milk and Urine from Cigarette Smoking, *J. A. M. A.* 120: 1003, 1942.

The authors review the literature pertaining to the effect of nicotine upon babies and its concentration in the breast milk and urine of cigarette smoking mothers. Mothers were divided into groups of occasional, moderate, and heavy smokers. Nicotine was found present in every specimen of milk and urine obtained from mothers who smoked cigarettes. A definite correlation between the number of cigarettes smoked, and the quantity of nicotine secreted in the milk and urine was found. The main excretion of nicotine was found in the milk and urine 4 to 5 hours after smoking. About 11 to 1 times as much was excreted in the urine as in the milk. It was found that lactation was little, if at all, affected by smoking. Nurslings were unaffected by the quantity of nicotine injected. The authors state that the absence of any demonstrable deleterious effect of nicotine on lactation and on the infants may be due to the development of a tolerance to the drug. All of these mothers smoked during their pregnancy. The infants were exposed to the nicotine in their mothers' blood while in utero, and likewise had the opportunity to develop a tolerance to the drug.

WILLIAM BERMAN.

Venereal Diseases

Axelrod, S. J.: The Diagnosis of Lymphogranuloma Venereum, *Am. J. Syph., Gonorr., & Ven. Dis.* 26: 474, 1942.

1. There is admittedly great difficulty in evaluating an intradermal test method when there exists for lymphogranuloma venereum no absolute diagnostic criterion which at the present time is practical for routine use.

2. Some of the difficulties inherent in the use of an antigen for intradermal testing made from other sources (e.g., mouse brain or human bubo pus) may be overcome by the use of a virus antigen made from a suspension of the virus of lymphogranuloma venereum cultivated in the yolk sac of the chick embryo.

3. Consideration of the case material studied, the virus antigen in question gives results consistent with the history or the clinical findings or both in a high percentage of cases.

4. The virus antigen used is apparently no less sensitive than the potent human bubo pus antigens with which it was compared.

5. The administration of sulfanilamide to cases of the anorectal form of lymphogranuloma venereum may, in certain instances, cause the disappearance of the specific skin sensitivity found in this condition.

6. In four cases studied neither intrauterine infection with the virus of lymphogranuloma venereum nor transplacental transmission of antibodies to the Frei antigen, as determined by intradermal testing, was demonstrated.

7. Nonspecific positive reactions to normal chick embryo control occur in a small percentage of cases. Normal chick embryo control should be used in every case tested with the virus antigen.

C. O. MALAND.

Beerman, Herman, Wammock, Virgene Scherer, and Magnuson, Kathryn Bause: Third Generation Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* 26: 504, 1942.

Third generation syphilis, if it exists, must be uncommon since most of the reported cases fall down when subjected to critical analysis and the strict criteria of Fournier and Finger.

A case is presented which fulfills most of the Fournier-Finger criteria.

C. O. MALAND.

Anatomy, Abnormalities, etc.

Klingensmith, Paul O., and Barden, Robert P.: The Obstetric Significance of Anatomic Variations in the Inlet of the Female Pelvis, *Pennsylvania M. J.* 44: 891, 1941.

Roentgenographic data was correlated with the clinical history of 580 patients selected on the basis of anticipated or actual dystocia. Study of the anatomic variations of the inlet of the female pelvis was applied to the problem of failure of engagement of the fetal head at term. Correlation of the true conjugate diameter with the shape of the pelvic inlet gave the most satisfactory type of analysis of the authors' material.

When the true conjugate was less than 9.0 centimeters, the term fetal head did not engage in any instance. Fortunately, a pelvis this small was seen in only twelve patients. When the true conjugate was from 9.0 to 9.9 centimeters, flat pelvises were much more efficient than gynecoid or android pelvises. In this range anthropoid pelvises did not occur in significant numbers. When the true conjugate was over 10.0 centimeters, only the android types were associated with a high incidence of cesarean section. When over 11.0 centimeters, even an android pelvis may be expected to accommodate the fetal head.

The remarkable efficiency of anthropoid pelvises was due to their large size; not only were the true conjugates long, but the transverse diameters were under 11.0 centimeters in only 8 per cent of the authors' patients. No correlation between the degree of inclination of the pelvic inlet and failure of engagement of the fetal head could be established.

J. P. GREENHILL.

Doyle, James C.: Imperforate Hymen: With and Without Hematocolpos, California & West. Med. 56: 3, 1942.

A review of the literature and a report of twenty cases is given. The embryologic development of the hymen is reviewed in an attempt to explain the etiology of imperforate hymen. The pathologic changes range from hematocolpos to hematometra, to hematosalpinx, to hemoperitoneum. Symptoms and clinical findings depend upon the age of the individual and whether it is a pubertal or a post-pubertal finding. The findings of an acute urinary retention seem relatively frequent in these cases.

The treatment is surgical and should be carried out in a hospital. The author recommends the injection of a solution of sulfathiazole through the hymeneal membrane before the actual incision is made. Laparotomy to remove a poorly draining hematosalpinx should be performed only if symptoms require it. The most common complications are postoperative cicatricial stenosis, hemorrhage from the cut end of the hymen, and ascending infection leading to peritonitis.

WILLIAM BERMAN.

De Oliveira Figueiredo, Ivan: Anomalous Vestibular Anus in a Parturient Woman, Rev. Med. Municipal, Rio. 3: 53, 1942.

The author reports in detail his conduct of the labor of a woman having a vestibular anus. This is his second case in a series of 1,300 labors; previous reports giving the incidence as 1:73,000 labors. The levator ani muscles were hypertrophied. Local anesthesia of the perineum was obtained by nerve block. With the application of outlet forceps, preparation was made for wide lateral incision of the vagina to preserve the integrity of what rectovaginal septum was present. The infant was expelled without incident and the puerperal course of the mother was normal. The possibilities of infection due to the anomalous opening are discussed. Expert prenatal care was, no doubt, an important factor in the successful outcome.

R. J. WEISSMAN.

Gynecologic Operations

Borras, P. E.: Surgical Treatment of Uterovaginal Prolapse, Bol. soc. de obst. y ginec. de Buenos Aires 21: 666, 1942.

This subject is discussed by the author on the basis of a review of 589 cases operated upon at Hospital Español and Catedra de Ginecologia of the Hospital Centenario from 1912 to 1942. The Halban operation was performed in 293 cases; the Fothergill, in 145; there were 64 hysterectomies for prolapse and 28 cystopexies by Ward's method. The remaining operations were other techniques (a few cases) and procedures that were performed in the first period, before the Halban operation was used. The surgical results following the Halban and Fothergill procedures were highly satisfactory. There were practically no recurrences, and the patients were well pleased with their improvement. There were 5 recurrences following the Halban operation and two following the Fothergill operation. Postoperative complications included hematoma of the lateral vaginal wall in one case; hemorrhage, 2 cases; cystitis, 8; febrile reactions, 3; phlebitis, 1 case; cardiovascular failure, 1 case. There were two fatalities. Four patients have had pregnancies and deliveries following operation.

All types of anesthesia were employed in the beginning. Local anesthesia with adrenalin, used later, is usually complete and satisfactory. Actually spinal anesthesia with novocain was used in the majority of cases, infiltrating the vaginal tissues with

adrenalized anesthetic solution. This anesthesia has the advantage of producing a maximal relaxation of all the pelvic muscles, lasting throughout the operation.

The author concludes that the statistical data do not give the complete picture, because clinical observation of these cases shows that the Halban or Fothergill operations have solved the problem of uterovaginal prolapse of all grades of severity, and that from the practical point of view, the potential mortality and morbidity offer no contraindications.

J. P. GREENHILL.

Bazan, J., and Althabe, O.: Fothergill Operation in the Treatment of Genital Prolapse, *Semana méd.* 49: 1476, 1942.

The authors report results of the Fothergill operation in 314 cases of genital prolapse, of varying degrees. The immediate results in general have been good. It has been possible to re-examine only 94 of the 314 patients operated upon, at times varying between ten months and five years after operation; in one case, examination was made nine years after operation.

The patients' ages varied from 25 to 60 years. In 87 of the 94 patients followed, the result was satisfactory, surgically as well as subjectively, and the patients, besides not having any recurrence of the prolapse, had felt very well after the operation. Seven failures were observed. From the viewpoint of later pregnancies, the Fothergill operation offers definite and appreciable advantages over other techniques, as was demonstrated in eight cases in this series, in which pregnancy occurred one to five years after operation and was terminated normally.

The anesthesia employed in this series always was local.

J. P. GREENHILL.

Leon, J.: Electrotomy. Histologic Changes Produced by It in the Genitalia and Other Organs, *Arch. Clin. obst. y gynec.* "Eliseo Cantón" 1: 731, 1942.

Leon praises Hyams' electric method of conical excision of the cervix. In addition to excising diseased portions of the cervix, it permits removal of pieces of tissue the entire length of the cervical canal for histologic study such as the cystic changes undergone by the endocervix. Animal experiments performed by the author showed that electric conization produced in the genitalia and other organs, not only a narrow zone of coagulation but also a series of changes in the adjacent tissue. These changes consist of a peculiar elongation of cells in the direction of the current and a palisade arrangement and pyknosis of the nuclei. Hence those who use the Hyams' electrode for biopsy in the female should familiarize themselves with the changes which occur in order to avoid error.

J. P. GREENHILL.

Jacobson, Philip: Further Experience With Tubal Division in Salpingitis, *Virginia M. Monthly* 70: 205, 1943.

Treatment of salpingitis by ligation of the Fallopian tubes near the uterine cornua is recommended in preference to salpingectomy. It is stated that the incidence of cure, the prevention of recurrence and the relief of pain are equal, following this simpler operation. It has the further advantage of preserving the vascular supply of the ovary, and it is therefore followed by no symptoms related to ovarian failure. The author feels that all cases of salpingitis should be so treated except where there is a unilocular inflammatory cyst of the ovary in which case the ovary should be removed.

WILLIAM BICKERS.

Soule, S. D., and Bortnick, A. R.: Mapharsen in Syphilis Complicated by Pregnancy, *J. Missouri M. A.* 40: 97, 1943.

It is a well-known fact that syphilitic pregnant women tolerate treatment with arsenicals exceptionally well. When adequate treatment is given such women, they have almost as good a chance of delivering a normal child as the nonsyphilitic woman. What is adequate treatment for the syphilitic pregnant patient? The authors, in the obstetric unit of the venereal division of the Washington University Clinics, have given a very clear and concise discussion of their method, procedure and results. They have used mapharsen and lipobismol since 1940, during which time 500 syphilitic pregnant women have passed through the clinic. This report is based on 100 of these cases whose babies were available for study at the age of 3 months. Of these 100 cases, 84 were seropositive and 16 seronegative. Sixty-five of the 84 seropositive mothers delivered normal babies, and 19 of this group terminated disastrously. Of the 16 seronegative group, 14 obtained normal children and 2 terminated disastrously—a total loss of .21 per cent. Among the seropositive group (84) 22.7 per cent terminated in fetal death as compared to 12.5 per cent among the seronegative group of mothers (16).

The average number of treatments for the group was 11.5, and the total average dose of mapharsen per pregnancy was 384 mg. The average single dose was 0.034 Gm.

The need for early initiation and adequate amount of treatment is very strongly recommended.

HARVEY B. MATTHEWS.

Foss, Harold, L., and Babcock, Reed J.: Total Abdominal Hysterectomy, *Surg., Gynec. and Obst.* 76: 214, 1943.

The authors report 156 total abdominal hysterectomies performed according to an original technique designed by the senior author. The first part of the paper contains a brief review of the literature concerned with the argument of total versus partial abdominal hysterectomy. The much argued questions of mortality, morbidity, and the occurrence of stump carcinoma are briefly discussed. The authors stress the technical difficulties of the total operation, and the need of a well trained surgeon in order to obtain satisfactory results. Finally the authors' operation is described in detail. This differs from the classical procedures in two main points. Two new instruments are described, one a right-angle knife, for cutting across the vagina, and the other a right-angle clamp, somewhat resembling a kidney pedicle clamp for closing the vagina prior to dividing it. The drawings of the various steps in the operation deserve especial commendation.

L. M. HELLMAN.

Bigelow, W. A.: A Study of the Results Obtained by Section of Ovarian Vessels and Adjoining Tissue in the Relief of Certain Types of Pelvic Pain, *Canad. M. A. J.* 47: 233, 1942.

The author reviews thirty-eight cases complaining of pelvic pain believed due to (1) pelvic varicocele or enlarged veins in the broad ligaments or ovarian veins, (2) painful sequela of thrombophlebitis of these veins, (3) the occasional persistence of pain after the removal of ovarian tumors. The pain is characterized as being low in the side, throbbing and bearing down. It is exaggerated on standing. In twenty-nine cases it increased premenstrually.

Thirty-seven of these patients were cured by laparotomy during which the ovarian vessels and surrounding sympathetic nerves are doubly ligated and transected through an incision made in the peritoneum at a point between the common iliac vessels and the suspensory ligament of the ovary.

CARL P. HUBER.

Labor, Physiology, Management, Complications

Ahumada, J. L., and Diradourian, J.: The Dangers of Infection Through Manual Removal of the Placenta, *Arch. Clin. obst. y ginec.* "Eliseo Cantón" 1: 792, 1942.

The authors analyze 702 cases of manual removal of the placenta, from the Eliseo Cantón. The incidence of manual removal at this institution was 1.33 per cent. The total mortality was 8.1 per cent, of which deaths from sepsis occurred in 3.3 per cent. The more infected the cases were at the time of manual removal, the graver was the prognosis. The authors therefore emphasize that, while this manipulation is relatively harmless in nonfebrile cases, it is serious in women who are infected. In view of this, the danger of manual removal of the placenta as an operative procedure has been greatly exaggerated. Because of this, a placenta should be removed early in the presence of serious hemorrhage.

J. P. GREENHILL.

Cootz, A. S.: Prognosis in Premature Rupture of the Membranes, *Arch. Clin. obst. y ginec.* "Eliseo Cantón" 1: 818, 1942.

Author maintains that premature rupture of the membranes has an unfavorable prognosis because it results in interruption of gestation prematurely and it may lead to amniotic infection. Furthermore, the following disturbances may follow premature rupture: anomalies in uterine contraction, increase in complications of the third stage of labor, greater frequency of operative interference and unfavorable effect on the fetus. There is also an increase in morbidity and mortality during the puerperium.

J. P. GREENHILL.

Beruti, J. A.: Antispasmodic Treatment During Spontaneous Labor and Its Effect on the Fetus, *Arch. Clin. obst. y ginec.* "Eliseo Cantón" 1: 699, 1942.

Beruti administered spasalgine and chloral hydrate to groups of women in labor and studied the effects of these drugs on the babies. In the cases of spontaneous labor, spasalgine had no bad effects on the babies. In a second group chloral hydrate was given to women who were having prolonged and difficult labor and again the babies fared well. The author compared the effects of spasalgine and chloral hydrate and concluded that chloral hydrate is probably less harmful to the newborn than spasalgine.

J. P. GREENHILL.

Higgins, L. G., F.R.C.S.: Cesarean Section in Dystocia, *Brit. M. J.* 4285: 212, 1943.

Higgins suggests "that the operation of Cesarean section involves less risk than difficult vaginal delivery, and that the indications for abdominal delivery may be considerably extended with advantage to mother and child."

He reports two series of personal cases, making 220 in all, which have been operated since 1931. One is a series of 157 elective operations; the other comprises 63 operations performed late in labor.

He gives some statistics describing his operative technique, compares results with series of forceps deliveries, and closes with the following summary and conclusion:

A personal series of 220 cases of cesarean section by the lower-segment technique is reported and briefly analyzed. A consideration of this and other reported series

suggests that the maternal mortality rate in this operation should not exceed one in three hundred.

The consequences of forceps delivery are considered and the unsatisfactory results for mother and baby are pointed out. In view of the encouraging results of cesarean section, the legitimate indications for forceps delivery require careful review.

The outlook toward cesarean section should be completely readjusted, and the operation must be used much more freely in serious dystocia to avoid the maternal and foetal morbidity often reported.

F. L. ADAIR.

Walker, C. W., M. C., M.D.: *Pregnancy and Labor in a Case of Congenital Coarctation of the Aorta*, Brit. M. J. 4284: 190, 1943.

Walker reports in detail the case history of a woman of 31 in whom congenital coarctation had been diagnosed eleven years before. She came to him when pregnant for the first time. The labor culminated in an emergency second-stage forceps delivery of a five-pound fetus.

The author makes the following comments:

The decision to allow labor to continue rather than have early recourse to cesarean section was prompted by the following considerations: the patient felt strong and well, was calm and confident, and was anxious to make the attempt; the infant was small and its presentation normal (L.O.A.), so that its passage might reasonably be expected to be an easy one; the early progress of cervical dilatation was free from fatigue and cardiac distress. In spite of these favorable circumstances the labor had to be stopped as soon as second-stage pains set in, as it was obvious that the tension in the upper circulation was being dangerously raised. With a full-time child, a less favorable presentation, a maternal heart having less reserve, or in the presence of more distressing first-stage pains, the danger-point might well be reached before dilatation was complete and delivery possible. This being so, it would appear that in cases of coarctation of the aorta, however favorable, the obstetric procedure of choice is cesarean section at the onset of labor.

F. L. ADAIR.

Pregnancy, Physiology, Diagnosis

Echevarria, R.: *Pregnancy and Parturition in the Primipara Over 40 Years*, Bol. soc. de obst. y ginec. de Buenos Aires 21: 489, 1943.

The author discusses the problem of the aged primipara on the basis of 98 cases, seen from 1912 to 1941, among 29,710 cases at the Instituto de Maternidad (Buenos Aires). The majority were between 40 and 45 years, but there were two aged 46, one 48, and one 49. Only 46 patients were observed during pregnancy. Complications of pregnancy included pruritus, albuminuria, edema, hypertension and eclampsia (5 cases). There were two fetal deaths, one due to syphilis and one to kidney disease. Twenty births were premature, eight at 8½ months, three at 8 months, and nine at 7½ months. By rare coincidence the two oldest patients had short labors, but in most of the group it was prolonged. Internal version was done three times; abdominal cesarean operation, four times; vaginal cesarean, twice; a large pelvic extraction, once; and embryotomy for dead fetuses, twice. Maternal mortality was 5 cases and fetal mortality 24 cases. Male offspring predominated (62.5 per cent).

The author concludes that in the primipara over 40 years, toxemia is much more frequent as a probable result of greater instability of the vital organs; labor progresses more slowly because of uterine inertia and greater resistance of the birth canal to the passage of the fetus; and there is a greater number of difficult births because of the same uterine immobility. For these reasons, the number of obstetrical and surgical interventions is increased, which in turn increases maternal morbidity and fetal mortality.

Hence medical vigilance during pregnancy of an aged primipara should be especially rigorous. When labor begins, careful observation should determine the degree of uterine motor function, and measures should be instituted to increase this. Pituitary preparations and antispasmodics are sometimes valuable in aiding dilatation of the cervix and thus shortening labor. The cesarean operation has wide application in these cases, when uterine immobility is combined with other complications, such as abnormal presentation and tumors.

J. P. GREENHILL.

D'Amour, Fred E.: A Comparison of Methods Used in Determining the Time of Ovulation, *J. Clin. Endocrinol.* 3: 41, 1943.

Starting with the basic assumption that ovulation usually occurs during the mid-interval and is under hormonal control, twenty menstrual cycles in five women were studied in order to compare the results obtained by applying concurrently four to six indirect methods for ascertaining the time of ovulation. The six methods applied were gonadotropin assays, estrogen assays, pregnandiol assays, vaginal smears, body temperatures, and subjective symptoms. Accepted methods of procedure were used for assaying complete 24-hour specimens of urine, no sample of which stood more than 48 hours before being used. Vaginal smears were recorded according to the interpretations of Rubenstein. Daily body temperatures were taken vaginally before arising. Subjective experiences were recorded in a notebook by each individual.

Four charts are presented, the first being a composite chart recording concurrently for each cycle a comparison of the vaginal temperatures, the vaginal smears and the assays from each subject on the basis of data of equal strength. The remaining three charts record quantitative results of the gonadotropin, estrogen, and pregnandiol assays respectively.

A detailed consideration of the various results leads to the conclusion "that (a) subjective experiences were valueless as tests for ovulation; (b) body temperature fluctuations were not sufficiently regular or clear cut to be reliable; (c) the uniformity of the results of hormonal assays and vaginal smears confirmed the validity of each and a certain sequency of events appears typical of the normal cycle; (d) because of its sharpness and its apparent close association with ovulation, the gonadotropin peak occurring in the mid-interval was considered as most indicative of the exact time of ovulation."

CLAUDE J. EHRENBURG.

Sampson, John L.: The Work Imposed Upon the Heart in Pregnancy and Labor, *West. J. Surg.* 51: 107, 1943.

Within the last 15 years, there has been an abrupt drop in maternal mortality from heart disease. This improvement is the result of cardiac obstetrical clinics where early diagnosis and supervision of the heart lesion by internists and obstetricians are made possible. A report on 80 cardiac obstetric cases without a mortality is presented by the author.

In pregnancy there is a 45 per cent increase in blood volume during the ninth lunar month. This is largely plasma increase. There is an increased cardiac out-

put of 25 per cent and an increased oxygen utilization with a decrease in the relative amount of oxygen used from the mixed venous blood. All of these factors increase the circulatory burden. The most important is the increased plasma volume which reaches the height in the ninth lunar month and at this time incidence of cardiac failure is greatest. The fall in blood plasma volume in the tenth lunar month is accompanied by a drop in maternal mortality.

Oxygen consumption was studied by the author before, during, and after labor. Consumption roughly paralleled the estimated amount of work done by the uterus. Venous pressure studies showed elevation during labor which persisted for some hours into the postpartum period. It is therefore dangerous to give intravenous fluids during the late stages of labor or early postpartum period. Venesection should be considered as a lifesaving measure in impending heart failure. No answer to the question of cesarean section in cardiacs can be given but it is hoped that the evidence presented by these studies on oxygen consumption will open the way for more intelligent discussion of this problem. A great amount of work is placed on the heart by labor even in multiparous deliveries.

WILLIAM BICKERS.

Pregnancy, Complications, Toxemia

Sosa y Sanchez, A. I.: *The Puerperal Myomatous Uterus*, Rev. méd. latino-Am. 28: 98, 1942.

The author is opposed to all surgical interference except that which is necessitated by urgent and serious indications. If myomectomy becomes necessary during gestation, there should be a minimum of manipulation. The author advises against removing fibroids at the time of cesarean section because it increases the risk to the patient. It is best to leave the myomas, because they do no harm, and remove them at a later date.

J. P. GREENHILL.

Lescher, F. Graham: *The Grave Anemias in Pregnancy and the Puerperium*, Lancet 2: 148, 1942.

A series of seventeen cases of grave anemia associated with pregnancy are reported. Nine were temporary pernicious anemias and eight were hemolytic. In eight cases the symptoms and signs of the anemia started before delivery, generally in the last three months of pregnancy, and progressed after parturition. In the remainder the anemia developed suddenly after the confinement. No patient had received adequate antenatal supervision and treatment and no blood examinations had been made before admission to the hospital. It is important to determine the type of anemia before beginning treatment because there is a specific treatment for each of the types described. The temporary pernicious anemias respond to liver therapy. The hemolytic anemia group respond to blood transfusion.

CARL P. HUBER.

Fullerton, H. W., M.D., M.R.C.P.: *Macrocytic Anemia of Pregnancy and Puerperium*, Brit. M. J. 4283: 158, 1943.

Fullerton reports three cases of macrocytic or so-called "pernicious anemia" of pregnancy which is usually assumed to be due to: (a) depression of the secretion of an intrinsic factor; (b) deficient intake of an extrinsic factor; (c) diversion to the fetus of the anti-anemic principle. The accepted treatment is that of the Addisonian type of pernicious anemia except that after the pregnancy recovery makes further treatment unnecessary.

The author's experience with the three cases leads him to state that "there was little or no improvement in the blood level after liver extracts given parenterally, but rapid regeneration occurred when this treatment was supplemented by the ingestion of whole liver."

The author reports his cases in some detail with charts and draws an analogy between these cases and others of similar type which he observed in association with steatorrhea.

F. L. ADAIR.

Hamilton, H. A., and Wright, H. P.: Development of Hypochromic Anemia During Pregnancy, *Lancet* 2: 184, 1942.

Repeated hemoglobin estimations by the Haldane method have been carried out on 392 pregnant women from about the third month of gestation until term. Half of the women examined were treated with medicinal iron throughout the period of observation, while the rest had no such medication. The average initial hemoglobin percentages were 79 in the untreated and 75 in the treated group. The corresponding average terminal percentages were 70 and 77, so that iron administration converted a deterioration during pregnancy into an improvement. From comparison with other published figures it is concluded that women of the artisan class are more anemic than before the war. Iron preparations should be given as a routine during pregnancy and antenatal clinics should help expectant mothers to select and prepare iron-rich diets.

CARL P. HUBER.

Society Transactions

THE OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF APRIL 1, 1943

The following papers were presented:

Prolapse of the Intestine Following Abortion. Robert C. McElroy, M.D.

A Simple Device for the Approximate Determination of the Blood Loss Immediately Postpartum. Owen J. Toland, M.D.

A Massive Unruptured Tubal Pregnancy. Bernard Mann, M.D. (For Original article, see p. 580.)

Oliver Wendell Holmes and the College of Physicians. W. B. McDaniel, II (by invitation).

The Lactogenic Effect of Prolactin in the Human Being. Samuel G. Winson, M.D. (by invitation). (For original article, see page 545.)

NEW YORK OBSTETRICAL SOCIETY

MEETING OF APRIL 13, 1943

The following paper was presented:

The Development of the Human Vagina and Its Relation to Developmental Abnormalities. Robert Meyer, M.D. (by invitation).

MEETING OF MAY 11, 1943

The following paper was presented:

Severe Pre-eclampsia. Charles M. McLane, M.D. (by invitation). For original article, see page 549.)

Correspondence

Artificial Insemination

To the Editor:

This letter has been stimulated by Folsome's recent critical review of artificial insemination (AMER. J. OBST. & GYN. 45: 915, 1943). My letter has a threefold purpose.

1. I wish to congratulate Dr. Folsome and be numbered among the many who are supporting him in his protest against the publication of undocumented medical articles. Folsome's critical analysis of Seymour and Koerner's paper (*J. A. M. A.* 116: 2747, 1941), which dealt with an alleged survey of artificial insemination, is most timely and welcome. To my knowledge there were numerous physicians engaged in sterility investigations who were most astounded at the time with the publication of such incredible statements disclosed by the Seymour and Koerner report. However, it seemed that only a few of us ventured to discuss this report and their earlier reports frankly, deliberately and in open medical convention. Folsome's vibrant protest against the publication of such extreme unverified claims in artificial insemination and his plea for vigilance against the admittance of such undocumented "scientific" surveys to our medical periodicals, warrant the wholehearted support of the entire medical profession.

2. I wish to commend the editorial policy of the *American Journal of Obstetrics and Gynecology* for the freedom of expression not only in its "Original Communications" but also in its editorial encouragement of further discussion of such stimulating papers as the one written by Dr. Folsome. Such true freedom of the press deserves acknowledgment.

3. Notwithstanding my concordance with certain aspects of this subject I wish to express a difference in opinion from that apparently equally shared by Folsome and the Editor of the *American Journal of Obstetrics and Gynecology* with regard to the place or role of artificial insemination in the armamentarium of the physician treating sterility. While I agree with both these writers that the use of artificial donor insemination should be limited and of a selective nature, it seems that for the hosts of sterile men who at present desire a child they offer very little in its stead. Folsome suggests, that, rather than resort to artificial donor insemination we should spend more time seeking the causes of relative infertility and that as physicians our duty is prevention and reparation of sterility. The Editor of the *American Journal of Obstetrics and Gynecology* intimates that the "increasing knowledge about the physiology of human reproduction" has caused a diminution of the need for artificial donor insemination. While both these authors are correct in a sense, they offer nothing concrete to the physician who is at present faced with the immediate problem of a husband who is suffering with complete azoospermia and whose wife has been shown to be apparently fertile. While it is hoped that prevention of damage to the genital systems will in the future lessen the number of barren marriages, we are faced now, and will undoubtedly be faced in the future, with some men who are absolutely sterile and are unable to procreate.

Let us be frank and ask ourselves what can be done for the following list of unfortunate men whose semen reveal complete absence of spermatozoa.

a: The adult who has abnormally retained testes, or other congenital abnormalities.

b: The patient with endocrine disturbances who has not responded to present-day glandular therapy.

c: The unfortunate victim of a secondary orchitis following mumps.

d: The husband who suffers testicular atrophy and lack of spermatogenesis secondary to malaria and other exhausting fevers.

e: Those men sterile from x-ray and radium exposure.

f: Those unable to procreate as a result of trauma to the genital organs.

g: Those barren owing to bilaterally closed epididymides.

Can we stimulate spermatogenesis where it has faltered? It is almost universally agreed that in azoospermia, endocrines and the like have failed miserably in the treatment of deficient spermatogenesis. Can we, without hesitation, recommend surgery to alleviate sterility? One must admit that the operation of epididymovasostomy, and other similar operations, even in the best urologist's hands are considered far from satisfactory in the treatment of male sterility.

Is there anything that we can, at the present time, offer to the male who suffers with complete azoospermia?

In essence, we must confess that aside from legal adoption (which is surely not a medical solution) and the outside chance of surgical intervention we have nothing to offer the completely sterile husband. Until that time when medical science can offer more to the sterile husband the use of artificial donor insemination has its definite role in the treatment of the barren marriage.

ABNER I. WEISMAN, M.D.

817 WEST END AVENUE, NEW YORK CITY.

Erratum

In the article, "The Local Use of Acid Media and Sulfa Drugs in the Management of Cervicitis and Vaginitis" by Melvin A. Roblee, M.D., F.A.C.S., September issue, page 406, paragraph 5, line 10, type II should read *type III*.





Frederick Joseph Taussig
1872—1943

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In Memoriam

FREDERICK JOSEPH TAUSSIG

1872—1943

DR. TAUSSIG, a member of the Advisory Editorial Board of the JOURNAL since its founding, died of pneumonia August 21, 1943, at Bar Harbor, Maine, where he had gone a week before for a vacation following an operation in St. Louis on July 9 last. Though aged 70, convalescence was prompt and excellent, so much so that in five weeks he was able to depart on his vacation. Surviving are his wife, one married daughter, one son (Frederick Taussig, Jr., a Coast Guardsman stationed in Cleveland), two grandchildren, and a brother, the well-known internist Dr. Albert E. Taussig, of St. Louis.

Born in Brooklyn, N. Y., October 26, 1872, he came with his family to St. Louis at an early age. Graduated from Smith Academy, St. Louis, 1889, from Harvard University, B.A., 1893, and from Washington University, M.D., 1898. Interned for two years at St. Louis City Hospital for Women (formerly the "Female Hospital"), where he served as assistant superintendent, and then went to Vienna for further gynecologic study. Began private practice in St. Louis in 1902, and soon became associated with the Washington University School of Medicine, where he continued to teach. He advanced through the various instructor grades to Professor of Clinical Obstetrics and Gynecology, which position he attained in 1911 and graced with his splendid teaching ability and stimulating personality until his death.

An outstanding characteristic of Dr. Taussig was his tenacity of purpose in seeking the solution of difficult problems. This was manifested in his many useful activities, particularly in his attack on one of the most formidable problems in gynecology, namely, the effective treatment and prevention of vulvar cancer. Long ago when little hope could be given to patients with this disease, in which deep glandular involvement occurs so early, Dr. Taussig attacked the problem with

the true pioneering spirit of courageous enthusiasm and persistent industry. Through accurate recording of his cases and laborious pathological investigations and effective study of the same, he was able to establish definite information on which to base the plan of treatment which has saved so many of these patients and which is now standard for this disease. In prevention, likewise, his accurate methods and productive study established leucoplakic vulvitis as a large factor in the origin of vulvar cancer and excision of leucoplakic tissue as a decisive step in preventing the same.

Membership in scientific societies included American Gynecological Society (President, 1936), Central Association of Obstetricians and Gynecologists (President, 1932), American Medical Association (Section Chairman, 1911 and 1924), American Society for Control of Cancer, American Association for Cancer Research, American Radium Society, and the various local societies interested in gynecology and obstetrics. Hospital connections included Barnes, Jewish, Barnard Free Skin and Cancer, and St. Louis Maternity Hospitals. His consuming interest in cancer is shown by his leadership in the Missouri State Cancer Commission (of which he was Chairman and which founded the State Cancer Hospital at Columbia) and his productive work for the Barnard Free Skin and Cancer Hospital in St. Louis.

Dr. Taussig's extensive experience and study enabled him to do a great deal of informative and dependable writing. He is the author of two monographs, "Diseases of the Vulva" (1923) and "Abortion, Spontaneous and Induced, Medical and Social Aspects" (1935). He also made chapter contributions to Lewis' Surgery, Nelson's Loose-leaf Medical and Surgical volumes, Curtis' Obstetrics and Gynecology, Davis' Obstetrics and Gynecology, Brennermann's Pediatrics and Christopher's Surgery, in addition to numerous articles to medical journals through the years.

Dr. Taussig lived strenuously, usefully and happily his threescore years and ten, and his well-directed endeavors contributed materially to the advancement of effective practice in his chosen specialty.

H. S. Crossen.

Original Communications

A CONSIDERATION OF CERTAIN FACTORS PERTAINING TO THE CONTROL OF CARCINOMA OF THE CERVIX*

NORMAN F. MILLER, M.D., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan
Hospital)

AMONG the many battles being waged today is the struggle against cancer. On this front alone, in these United States of America, over 150,000 lives are lost annually. Cancer destroys more lives than the combined toll from tuberculosis, diabetes, appendicitis, cirrhosis of the liver, alcoholism, and automobiles. Thousands of these deaths are the result of cervix cancer, a special field of serious concern to us as gynecologists.

My own interest in this problem dates back almost a quarter of a century, to the time when radical hysterectomy offered the only hope for cure, while for inoperable cases, actual cautery through a water-cooled speculum was the palliative procedure of choice. To the early 'twenties, when irradiation was fighting for, and achieving, a rightful place as an important remedial weapon. Through a decade of confusion, when the carcinoma patient was an unwanted derelict, to an era of mounting interest and stabilized therapeutic methods. In 1931, with the inauguration of our Gynecology Tumor Conference at Ann Arbor, it became possible for us to study cancer of the female generative tract in a more formal manner. Since the beginning of this conference, we have carefully evaluated and treated nearly 2,000 carcinomas of the female generative tract.

Of this number, 65.8 per cent, or 1,235, were cervix cancers. All of these patients have been carefully studied and evaluated by our Conference group, which includes members of the gynecology staff, representatives from the department of roentgenology, and when possible, the pathologist. All lesions have been carefully examined, and the neoplastic nature microscopically proved. Except for a few seen shortly after our group was first organized, all of these cases have been clinically grouped and the neoplasms histologically graded. All patients have been followed. There are no untraced cases in our entire series. In recent years this tremendous follow-up task has been the achievement of our social service department. Twice weekly for the past eleven years, the conference group has met to evaluate individual

*Presented at a meeting of the Chicago Gynecological Society, April 16, 1943.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

TABLE I. ANATOMIC DISTRIBUTION OF 1,876 MALIGNANCIES OF THE FEMALE GENITAL TRACT SEEN IN THE GYNECOLOGY TUMOR CONFERENCE FROM JULY 1, 1931, TO DECEMBER 31, 1942*

ANATOMIC SITE	NUMBER OF NEO-PLASMS	PERCENTAGE OF ALL NEOPLASMS SEEN
Cervix	1235	65.8
Fundus	263	14.1
Carcinoma of Uterus (Site of Origin Unknown)	2	0.1
Ovary	158	8.1
Vagina	38	2.1
Vulva	83	4.4
Clitoris	8	0.4
Fallopian Tube	2	0.1
Bartholin Gland	1	0.05
Sarcoma of Uterus (Cervix or Body)	30	1.7
Carcinoma and Sarcoma of Uterus	4	0.25
Chorionepithelioma	10	0.5
Pelvic Malignancy Unclassified	39	2.2
Sarcoma of Vagina	3	0.2

*99 Consultation Only Neoplasms included in this Table.

patients and the problems pertaining to their classification, disposition, and treatment. Each year the results of this study have been recorded in statistical form, as the report of the Gynecology Tumor Conference. This living with the problem has been illuminating and instructive. It has crystallized thought, which now reappears as a dreary conviction that results are not what they should be, chiefly because of the long recognized fact that the disease is too far advanced when first seen. I shall have more to say about this obstacle to better survival rates, but first let us probe certain other pertinent factors.

On the Quality of Treatment.—The limitations of existing methods of treatment are well recognized. No one expects the impossible, but there is good reason to believe that therapy is disappointing. We appear to have reached that comfortable state wherein we hesitate to disturb the efficiency of a therapeutic system which has taken a long time to establish. Perhaps the ease of administration, as well as the apparent effectiveness of irradiation therapy, has lulled us into a state of inertia, in which we fail to exploit existing methods of treatment to their fullest capacity. In radical abdominal hysterectomy, as first performed by W. A. Freund in 1878, and later popularized by Wertheim, was recognized a potent weapon for combating cervix cancer. But, because of its high primary operative mortality rate, and its restricted field of usefulness, the operation was permitted to pass into the discard. Radium and x-ray have also proved their worth. Yet, after almost a quarter century devoted to the refinement of technique and stabilization of procedure, I find there is little to boast about. Inspection of Table II, showing a panorama of five-year survival rates since the turn of the century, reveals evidence of success, but in general the picture brews no optimism in my mind. Perhaps we have reached the end of an era. Perhaps if we could see into the future, we might visualize as the cancer therapist not the radiologist, not the gynecologist nor the surgeon, but possibly the chemist. It is not beyond the realm of possibility that

TABLE II. PANORAMA OF FIVE-YEAR SURVIVAL RATES

REPORTED BY:	YEAR	TYPE OF TREAT.	FIVE-YEAR SURVIVORS
Schuchardt ¹	1905	Surgery	*40.0%
Taussig ³	1912	Surgery	*41.6%
Neel ²	1912	Surgery	*35.0%
Cullen ⁴	1912	Surgery	*26.9%
Regaud ⁵	1923	Irradiation	45.0%
Healy ⁶	1924	Irradiation	20.0%
Heyman ⁸	1929	Irradiation	21.5%
Lynch ⁷	1931	Combination	*58.1%
Heyman ⁹	1931	Irradiation	*40.5%
Heyman ⁹	1931	Irradiation	23.1%
Healy ¹⁰	1931	Irradiation	22.0%
Crossen & Newell ¹¹	1932	Irradiation	22.3%
Delporte Cahen, & Sluys ¹²	1933	Irradiation	26.0%
Ward ²⁰	1933	Irradiation	21.6%
Bonney ¹³	1935	Irradiation	*55.0%
Schmitz ¹⁴	1935	Surgery	22.2%
Scheffey & Thudium ¹⁹	1936	Irradiation	25.3%
Bonney ¹⁵	1937	Irradiation	*39.0%
Shaw ¹⁶	1937	Surgery	*38.0%
Shaw ¹⁶	1937	Surgery	41.4%
Madame Curie Hosp., London ¹⁷	1937	Irradiation	36.2%
Plate, W. P. ¹⁸	1937	Irradiation	32.8%
Ward and Sackett ²¹	1938	Irradiation	28.5%
Kamperman ²²	1941	Irradiation	35.0%
Schmitz & Sheehan ²³	1941	Irradiation (High Voltage)	46.1%
Scheffey, Thudium, & Farrell ²⁴	1942	Irradiation (High Voltage)	23.1%
Miller (present article)	1943	Irradiation	35.1%

*Based on operable cases, therefore not absolute survival rates.

radium may some day become a drug on the market, and deep x-ray therapy equipment an excellent source of copper wire and other spare parts. The limited capacity of existing remedial measures is definitely responsible for some of our restricted success, but any attempt to blame results on this basis alone might more properly be attributed to an indolence on our part—a failure to exploit to their fullest efficiency radium, x-ray, and surgery, or a combination thereof—a serious failure to give these methods of treatment a fair chance. In this last connection, the ineffectiveness of concerted and energetic efforts at lay education plays an important role. In both irradiation therapy and surgery, we have potent weapons. Perhaps neither has been developed to its fullest efficiency. Given an opportunity, these methods may still accomplish what we have a right to expect in the way of vastly improved survival rates.

Clinical Grouping.—While not directly related to the problem of survival, clinical grouping is so intricately woven into the pattern of our present problem that it cannot be entirely dodged, shrink as we may from the thought of reopening this moot question. Inspection of five-year survival rates listed in Table II reveals a marked disproportion which may be attributed to variations in technique. More likely, however, the better results noted by some observers are largely due to the character of the material with which they work. In most clinics there is a preponderance of advanced cases but in some the disproportion

tion between early and late is not so pronounced. That there is an important difference in the character of material treated and that it colors results has long been recognized. Such differences may continue to exist, but it would help a great deal in the evaluation of end results if we were all bound by one standard and universally acceptable clinical grouping. Existing classifications are numerous. No single clinical grouping has

TABLE III. GROSS ABSOLUTE SURVIVAL RATES FOR CARCINOMA OF THE CERVIX (1,164 NEOPLASMS), UNIVERSITY OF MICHIGAN

YEAR OF ADMITTANCE	SURVIVAL PERIOD	ALIVE DECEMBER, 1942	
		NUMBER	PER CENT
1931	11 years	23	26.1
1932	10 years	86	19.7
1933	9 years	88	19.2
1934	8 years	111	20.7
1935	7 years	104	22.2
1936	6 years	121	28.9
1937	5 years	91	35.1
1938	4 years	108	53.1
1939	3 years	111	47.7
1940	2 years	89	48.3
1941	1 year	109	73.4

yet been devised that is entirely satisfactory to everyone. It is with this realization that I venture to broach the subject at this time. To justify universal acceptance, a clinical grouping of cervix cancer should be:

- A. Simple
- B. Practical
- C. Easily understood
- D. Clearly defined
- E. Based on actual physical findings and not on assumptions
- F. One that places emphasis on early cervix cancers, and not on the advanced lesions for which existing remedial measures prove so disappointing.

The most notable attempt to provide a grouping of this sort is seen in the League of Nations classification. This classification has not been universally accepted, due, I believe, to four main objections, namely, (a) it is too complicated, (b) it is impractical, (c) it does not sufficiently emphasize the early lesion, and (d) it does not recognize the physical impossibility of definitely determining at a certain stage of the disease, the presence or absence of parametrial spread. The Schmitz classification, on the other hand, approaches the requirements set forth above. It is simple, and it does recognize the impossibility of sharp differentiation at certain stages in the course of the disease. It does not, however, place sufficient emphasis on the early lesion—that stage which is amenable to remedial methods already in our possession. The weakness then of the Schmitz classification lies in its too inclusive, ill-defined first group. As an example of a clinical grouping which fulfills the requirements listed above, I present the following:

Carcinoma of Cervix

Clinical Grouping

	As Used at the University of Michigan Hospital
Clinical Group I	Very early carcinoma of the cervix. In general this group includes the early, suspicious, often unrecognizable clinically but histologically proved carcinomas of the cervix, i.e., intra-epithelial lesions and carcinoma arising in a cervical polyp, etc.
Clinical Group II	Any clinically recognizable histologically proved carcinoma still confined entirely to the cervix. No parametrial thickening.
Clinical Group III	Carcinoma of the cervix with questionable parametrial thickening. The cervical lesion may or may not be extensive, the characteristic feature of this group being the question concerning parametrial involvement. Into this group are placed those patients concerning whom there might well be a difference of opinion regarding the involvement of adjacent tissues.
Clinical Group IV	All advanced carcinomas of the cervix. Those with definite parametrial thickening, vaginal infiltration, frozen pelvis, etc. (May be subdivided for statistical purposes.)

TABLE IV. COMPARISON BETWEEN UNIVERSITY OF MICHIGAN AND OTHER CLINICAL CLASSIFICATIONS OF CARCINOMA OF THE CERVIX

UNIV. OF MICH.	LEAGUE OF NATIONS	SCHMITZ
I	I	I
II	I	I
III	-	II
IVa	II	III
IVb	III	IV
IVc	IV	IV

This clinical grouping was designed to meet specific requirements. It incorporates the desirable features of many classifications, and has proved its practicability and adaptability in our clinic.

I have no desire to dwell on this subject beyond repeating that a practical, simple, easily understandable, and universally acceptable clinical grouping for cervix carcinoma is essential. Without such, comparison of survival rates is destined to remain a matter of confusion.

On the Causes of Death.—Survival rates and cure rates are not synonymous. While we aim to cure, we must frequently be satisfied with prolonged survival. Many patients reported as free from evidence of the disease still have it, but they probably will not die from cancer, for patients with cervix cancer seldom die as direct result of the neoplasm itself. Instead death comes through the intervention of secondary causes. In an analysis of the deaths amongst our carcinoma patients soon to be reported by Dr. Russell deAlvarez, it was noted that in 66 per cent of the cervix cases death was the result of uremia, and/or impaired renal function caused by encroachment of the neoplasm or scar tissue upon the ureters. This work is more than a confirmation of what we have known for a long time, for it suggests an opportunity for palliation, for the prolongation of the patient's life by circumventing death due to renal dysfunction. Specifically, uretero-intestinal anastomosis looms as a possibility in these cases. To carry out this opera-

tion in these patients would necessitate a modification of both present-day indications and technique. If contemplated, the operation should not be delayed to the point of making it a sacrificial procedure. The likelihood of adding years of usefulness and of comfort to the patient's life appears well within the realm of possibility. Every experienced worker in the field of cervix cancer has had ample opportunity to observe the marked subjective improvement and the continued survival of once incapacitated patients following timely colostomy. Perhaps diversion of the urinary stream may similarly lead to a measurable addition to the life span of the afflicted individuals. When bowel obstruction is evident, uretero-intestinal anastomosis would probably be ill advised, although this is a matter for future evaluation. As a means of prolonging life, the possibility of uretero-intestinal anastomosis and ureterostomy may well deserve comprehensive study and trial.

On Lay Education and Early Treatment.—Lay education to the point of developing a symptom consciousness has long been considered our best approach to the problem of cancer control. In cervix cancer, this channel would permit early treatment and possible prevention of so-called precancerous lesions. The wisdom of lay education cannot be doubted. Next to a perfect cure—which we do not now possess—lay education offers the greatest opportunity for reducing the annual toll from this disease. All effort expended in this direction is for a worthy cause and it sounds well to say that such effort is never wasted. The facts reveal, however, that a tremendous amount of painstaking and conscientious work in this connection has been wasted. It may be recalled that in the heyday of the radical hysterectomy, the operability rates varied from 20 per cent (Taussig 1912) to 54 per cent (Cullen 1912). Since it is estimated that the chances for survival in cervix cancer decrease at the rate of 16 to 20 per cent per month after the appearance of untoward symptoms, these early operative rates probably indicate a time lapse of three to five months from the onset of the first symptom to the time of treatment. In 1933, I reported an average time waste of 6.2 months prior to the patients seeking medical advice. In 1941, R. M. Collins noted an average time waste of 7 months between the onset of the first symptom and the first examination. Oliver Todd, in 1941, reported a pretreatment time loss of 6.4 months. Perusal of patients admitted to our clinic during the past two years shows no improvement over the figures given above. When we consider the elaborate programs carried on by national, state and county organizations directed specifically toward the elimination of this time waste factor, the results of these efforts cannot be considered very encouraging. Further evidence in this connection is to be found in Table V showing no increase in early cases seen by us, but a definite increase in the number of advanced lesions.

While this discouraging picture is not pleasant to contemplate, the work of the many men and women who have fought this problem has not necessarily been in vain. Such cold evaluation of lay educational achievement may be brutal, but it is necessary if we are to inject new life into this extremely worthy cause. Scientific exhortation reaches few women and confuses most of them. Talking and preaching the gospel of periodic examination is sound enough but so far it continues to be only a worthy objective. The pictured hazards of neglecting untoward symptoms have been more fruitful in their accomplishment than the

spoken or printed word. As a step in this direction, I should like to present for your consideration a color film, designed for lay consumption. It is my intention to make this film available to any physician, to be used by him as he sees fit in the visual campaign against cervix cancer. Much of the failure in lay education can be attributed to misunderstanding and bewilderment. Many women are not sufficiently familiar with their own anatomy to know where the cervix is located, and most lay women are totally in the dark and completely confused by mention of such terms as erosion, cervicitis, and cystic change. Just what sort of a visual image of the cervix and the diseases to which it is heir our best

TABLE V. CARCINOMA OF THE CERVIX BY CLINICAL GROUP AND YEAR OF ADMITTANCE

CLINICAL GROUP	1931		1936		1942	
	NO.	%	NO.	%	NO.	%
1	1	4.2	7	5.5	7	5.7
2	3	12.5	14	11.0	10	8.2
3	7	29.2	32	25.0	18	14.8
4	13	54.0	74	58.0	86	71.1

educational efforts have produced in the minds of our patients is something for the psychiatrist to determine. If the cervix were clearly visible, the problem of maintaining its health would be non-existent. Once women see what the doctor sees—once they visualize changes likely to exist in the cervix, the obstacle to early and wholehearted co-operation will in large measure be overcome.

Discussion

DR. HAROLD O. JONES.—Dr. Miller's statistics, as well as those of other clinics, establish the fact that not a single variation in the technique of treatment of carcinoma of the cervix has been submitted during the last ten years which has in any way reduced the final death rate. We are all seeing patients with about the same degree of involvement of the parametrium as of ten years ago and submitting them to an almost routine treatment.

It is with envy that I read of Dr. Miller's 100 per cent "follow up," but we have been aware of the thoroughness of his organization for some time. This has made all of us realize the statistical and scientific soundness of reports emanating from this group. The clinical classification offered by Dr. Miller has all of the advantages claimed for it by the author, in particular simplicity and workability.

The study of any group of patients after treatment for carcinoma of the cervix, yields the highest percentage of cures in Group 1. This leads the author to conclude that the only steps which will in *any* way influence favorably the percentage of cures, will be such procedures as will place more of these patients in Group 1. The real theme of this paper then is the need of furthering the education of the laity to the end that much earlier in the course of this disease the patient will present herself.

DR. HERBERT E. SCHMITZ.—That the diagnosis and management of the patient suffering from cancer is best carried on by an organized tumor group, as described by our essayist, is an accepted fact. The cooperation of the gynecologist, pathologist and radiation therapist assures the sufferer a correct diagnosis and a well thought out plan of treatment. Such a group must have at its disposal all known means of diagnosing and treating cancer, whether by surgery, irradiation

therapy, or a combination of both. To employ a certain routine procedure or dosage in all cases is inadequate treatment. A basic plan may be acceptable, but variations in technique are necessary because of the extent of the tumor and the difference in response of certain cell types and individuals to irradiation. With the statement that therapy is disappointing, I cannot agree. Reports are appearing quite regularly describing changes in dosage, filters, applicators, and methods of application of both radon and radium element. X-ray therapy with the perfection of apparatus during the past ten years has gone to higher and higher voltages. Numerous investigators are combining surgical procedures with irradiation therapy to increase the efficacy of the latter. When we consider that it takes five years at least accurately to evaluate a plan of treatment, then we cannot expect revolutionary changes to appear at frequent intervals.

In June of 1940, before the American Radium Society, I made the following statement in a discussion of clinical Classification of Cancer of the Cervix, "The evaluation of end-results in clinical cancer survey studies would be greatly facilitated if the method of classification employed were universal and constant in order that the greatest possible comparability between statements from different clinics could be secured." The Health Committee of the League of Nations, realizing that no such uniformity existed, has attempted to introduce a uniform classification. Few collaborators from this country have adopted this arrangement of cases, preferring to invent a clinical classification of their own or confusing a previous system by modifying it.

In Group I of the Schmitz classification are included lesions up to 1 cm. in circumference, whether proliferating or ulcerating lesions. Our objection to the same group in the League of Nations' classification is that it is too extensive. If we are to teach early diagnosis, then our early group must be confined to those lesions which, in our clinic, are diagnosed mostly by biopsy. The survival rate in this group is higher than in other groups and will aid us in impressing the laymen with the fact that early cancer is curable. In Dr. Miller's classification there is no definite demarcation between Groups I and II, there being a great variation in accordance with the examiner's ability to diagnose cancer. In Group IV, which has always been the far advanced, hopeless, and palliative group, he includes many cases which would respond to therapy, thus increasing the survival rate in this group. Until we all accept one classification there will be great variations in our end-results and further confusion in evaluating the different methods of therapy.

Inasmuch as early diagnosis is the key to increasing our good end-results, I am in hearty accord with any and all lay educational programs. Whether the patient will be impressed with these educational films remains to be seen. Tumors of the breast are easily felt and their growth frequently detected by the patient, but the period of delay before seeking the advice of a physician is about the same as for cancer of the cervix.

DR. J. P. GREENHILL.—In spite of the prevalent conception that chronic inflammation, chronic irritation and lacerations of the cervix are responsible for carcinoma of the cervix, there is no proof for this assertion. While cancer of the cervix may arise on the basis of a chronic erosion, such an occurrence is unusual. A large proportion of women have chronic erosions for many years and never develop carcinoma of the cervix. The chronic inflammation which is found around cancer tissue is not the cause of the cancer but the result of it. Examination of the earliest cancers shows that the inflammation is found only in the immediate neighborhood of the cancer and not at a distance from it.

Schiller found prosoplastic changes or excessive differentiation of tissue in 57 out of 60 early cancers of the cervix. Schiller considers these changes, and not

chronic inflammation, as the forerunners of carcinoma. In the mouse, substances which produce chronic inflammation alone and not prosoplasia do not produce cancer of the skin.

It is well known that carcinoma of the cervix occurs particularly in women who have had a number of children and it has been shown that the pituitary gland of multiparous women contains a diffuse hyperplasia of the eosinophiles of the anterior lobe. Likewise, such changes have been found in the hypophysis of many women who have uterine cancer.

Experimentally, changes which resemble carcinoma have been produced in the cervical epithelium by the injection of anterior pituitary hormone and by the implantation of pieces of pituitary gland. It has been shown by Hofbauer that the cervical epithelium both in pregnancy and in the nonpregnant state is under the influence of the pituitary gland. In fact, all the epithelium and only the epithelium of the female genital tract reacts to such hormonal stimulation.

Zondek found that anterior pituitary hormone was excreted in the urine of about 80 per cent of women who had cancer of the genitalia, whereas this hormone was absent in most individuals who had extragenital malignant tumors. Likewise, this hormone was found by Zondek and others in men who had carcinoma of the testicles but not in men who had cancer of the prostate. Hence, cancer of both the male and female genitalia creates special hormonal conditions. Engle found a positive Aschheim-Zondek reaction in all animals which had received injections of urine from cancer patients but negative reactions in all animals which received urine from patients with sarcomas. He concluded that there is a causal relationship between hyperfunction of the hypophysis and carcinoma.

There must be a constitutional factor involved in carcinoma of the cervix, else how can we explain the relative infrequency of these cancers in certain groups such as Jewesses who are as prolific as other women and hence have as much cervical irritation? How about carcinoma in nulliparas?

Belief in a hormonal or constitutional cause for cancer of the uterus does not imply that there cannot exist prophylactic measures against the disease. In order for cancer to arise, there must be not only a constitutional factor which is associated with cell growth and metabolism but also in most cases some local factor which at present is not definitely known. Hence it is essential that the cervix be maintained in as normal a condition as possible. This means that during labor, trauma to the cervix should be avoided and that after labor, all lacerations should be properly repaired. Furthermore, all women, especially those who have had a number of children, should have periodic visual as well as tactile examinations of the cervix. Abnormal conditions in the cervix, particularly vascular and granular areas, should be treated by some form of electrotherapy or operation in order to avoid hyperplasia, metaplasia and prosoplasia of the cervical and vaginal epithelium which, under stimulation by the anterior pituitary gland, may lead to carcinoma.

DR. EDWARD ALLEN.—It seems to me that both the paper and the discussions have graphically brought out the fact that we can cure cancer if we get it early. While this excellent picture may bring the adult woman with cancer phobia to the examiner, I think we are starting at the wrong end. We have educated the little girl from the age of three to avoid any examinations of her genitals. Until we know more about the cause of cancer, whether it be heredity or irritation, education of woman to seek and demand examination of her genitals from childhood up, seems the only logical approach. The obstetrician should start early, should start now, to educate mothers in methods of educating their daughters as to the importance of routine pelvic examinations rather than to wait for the premarital examination when it is next to impossible to examine adequately due to the psychic reaction.

I do not believe we will ever educate or frighten women by a national program into going to the doctor for examination of the genitals, if we start as late as eighteen or twenty years of age. What few patients I see in a small private practice with genital cancer, have hesitated to come for pelvic examination long after symptoms have begun. I think there are more cases of delayed examination in genital cancer than cancer anywhere else in the body. This is not because the cancer is out of sight but because women hate any examination of the genitals. We as gynecologists have seen no need of pelvic examinations unless the youngster has grave symptoms. I firmly believe that until we educate women to accept routine pelvic examinations from childhood and demand it from there on, we will get nowhere in our diagnosis of cancer. Maternal training has also affected the male so that many times doctors hesitate to do vaginal examinations especially in young patients,

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SOME DETERMINANTS OF MATERNAL AND PLASMA VITAMIN C LEVELS*

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A DETERMINANT, according to definition, is a circumstance or factor that, by itself or in combination with other circumstances or factors, fixes the nature of a result. In this study we shall consider the influence of pregnancy, labor, diet, season, hyperemesis gravidarum and other complications of pregnancy on the blood levels of vitamin C. In addition we shall examine the maternal-fetal relationship and some of its determinants. Since pregnancy increases the need for vitamin C, and since the exigencies of war have reduced the supply of natural as well as synthetic ascorbic acid, this aspect of nutrition in pregnancy is of timely importance.

According to available evidence the pregnant woman has a greatly increased need for vitamin C. Because of this, most investigators have reported that low maternal values are common during pregnancy.¹⁻⁸

Many believe that requirements for vitamin C increase progressively as pregnancy advances.^{5-6, 8-9} Under ordinary conditions there are two reasons for the increased needs of pregnancy: (1) Increased maternal metabolic activity, and (2) demands of the fetus and placenta. The fetus not only depends on the mother for vitamin C but also abstracts it at her expense. Consequently the fetal blood values are higher than maternal values^{2-8, 10-11} although some earlier workers, with less exact methods of analysis at their disposal, found little difference.¹³⁻¹⁴ The difference between maternal and fetal values is said to be greater when maternal values are low;⁴⁻⁵ or in other words, the fetal-maternal ratio is greater under such conditions even though absolute values are lower.

The daily requirements of vitamin C during pregnancy have not been accurately established.

Early estimates such as those of Widenbauer⁹ who recommended 28 mg. daily for the nonpregnant woman and 71 mg. daily during pregnancy, are obviously too low. The present tendency is to revise upwards the estimates of general adult requirements, which now are at approximately 75 mg. daily. Safe requirements for pregnancy have been placed at 100 mg. daily;¹⁵ however, if the pregnant woman's needs are double or treble those of the nonpregnant adult⁹ then the present standards for pregnancy appear to be too low. Javert and Stander⁸ estimated the requirements of pregnancy to be about 200 mg. daily, which is probably a more rational estimate. Teel et al.⁵ had great difficulty in maintaining a plasma concentration of vitamin C above

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1.0 mg. per cent during pregnancy even though attempts were made to improve the diet. Only when the values were low at the onset of pregnancy could they be improved with a better diet.

Methods and Plan of Study

All determinations of maternal and fetal blood vitamin C in this study were made according to the macrophotocolorimetric technique described by Mindlin and Butler¹⁶ but without the use of KCN as "antioxidant." The results are expressed as milligrams per 100 c.c. of plasma—mg. per cent.

Certain necessary precautions were always observed in collecting and handling the samples of blood. All were fasting samples obtained in the morning excepting, of course, those taken at the time of delivery. All women who had ingested vitamin C within four hours of delivery were excluded from this study. Fetal samples were obtained from the placental end of the umbilical cord *immediately* after delivery of the infant. Speed is important. The blood must be obtained rapidly without stripping the cord and mixed quickly with the potassium oxalate; failure to observe these precautions resulted in clotted or hemolyzed specimens. Furthermore, blood which remained in the placenta or umbilical cord for more than a few minutes gave abnormally high readings for vitamin C. We cannot say whether these high values were due to diffusion of stored vitamin from the placenta into the blood or to some extraneous reducing substances. Whatever the cause, such results were not valid.

In order to gain information about seasonal variations of blood vitamin C it was necessary to pursue the study through a two-year period. Furthermore, the study was planned so that each patient would have a determination of vitamin C during each trimester and at the time of delivery. This program was successful in most instances, though some patients went elsewhere or were "lost" to observation for one or another reason. Others were incompletely studied because they did not seek prenatal care until later in pregnancy. One hundred and ninety-seven women were observed at some time during pregnancy and forty-six were observed on three or more occasions.

The mother's intake of vitamin C was estimated from a careful review of her dietary history and on this basis she was placed into one of three classes *at each visit*. Thus it was possible for the dietary classification to change from time to time according to recent and current intake of vitamin C. There were three classes as follows: *Adequate diet*, which fulfilled the requirements for vitamin C set forth in the pamphlet "Prenatal Care":¹⁷ In brief, each patient on such a diet received at least two servings of green leafy vegetables daily (one of which was raw), and one or more servings of fresh fruit daily. Citrus fruit or juices and tomato juice were used as substitutes for or in addition to the fresh fruit. When the intake of vitamin C was below this

standard the diet was classified as *fair* or *poor*. The "poor" diet included few or no fresh fruits or vegetables. For example, a woman who had fresh fruits and vegetables but once or twice weekly would be classified in the "poor" dietary group. Those with intermediate intakes were classed as "fair." The general level of vitamin C intake is more readily estimated from dietary history than is the intake of any of the other food essentials.

Results

Maternal Studies

Vitamin C was determined on more than 500 samples of blood obtained from 197 women at different stages of pregnancy. Most of the samples came from the group of 46 women who were studied three or more times throughout pregnancy. The remainder were observed but once or twice during pregnancy and many of these were a part of the experiment which determined the maternal-fetal relationship of vitamin C at the time of delivery.

Diet.—Individual as well as group values of ascorbic acid were closely correlated with the type of diet. Table I lists the mean plasma vitamin C of women grouped according to the type of diet. About half of our determinations were for women with an "adequate" diet and the plasma level (0.95 mg. %) averaged within the optimum range. Fifteen per cent of the diets were "poor" and the mean plasma value was very low (0.18 mg. %). An intermediate average (0.52 mg. %) was obtained for the group with a "fair" diet. The results illustrate the wide range of plasma values which may be seen during pregnancy and which depend, to a large extent, on the diet. These results also show that it is possible to maintain high plasma values by means of an adequate diet alone.

TABLE I. SHOWING RELATIONSHIP BETWEEN PLASMA VITAMIN C AND TYPE OF DIET*

DIET	NUMBER	MEAN VALUE MG. %	STANDARD DEVIATION	STANDARD ERROR
Poor	45	0.18	± 0.092	± 0.0014
Fair	103	0.52	± 0.222	± 0.022
Adequate	152	0.95	± 0.252	± 0.022

*For dietary standards see above.

While we made no attempt to study extensively the effects of supplements of ascorbic acid, we did observe 24 women at delivery who, in addition to an "adequate diet" had received 25 mg. of ascorbic acid daily, contained in the commonly prescribed mixed vitamin preparations. The mean plasma values for these patients was 0.94 mg. % (standard deviation ± 0.196), while the value for 128 patients with adequate diet but *without* such supplements was 0.95 mg. % (standard deviation ± 0.26). These mean values are obviously without significant difference.

Season.—We have shown that vitamin C levels vary as the diet. The diet in turn varies with the season. In this latitude there are only four months during which the supply of fresh home-grown fruits and vegetables is abundant and generally available. These months are

TABLE II. SHOWING THE RELATIONSHIP OF DIET AND SEASON TO PLASMA VITAMIN C VALUES

VITAMIN C IN DIET	PERIOD A MARCH—JUNE						PERIOD B JULY—OCTOBER						PERIOD C NOVEMBER—FEBRUARY						TOTAL			
	INCIDENCE			VITAMIN C			INCIDENCE			VITAMIN C			INCIDENCE			VITAMIN C			INCIDENCE		VITAMIN C	
	NUM- BER	PER CENT	MEAN MG. %	ST. DEV.	NUM- BER	PER CENT	NUM- BER	PER CENT	MEAN MG. %	ST. DEV.	NUM- BER	PER CENT	NUM- BER	PER CENT	MEAN MG. %	ST. DEV.	NUM- BER	PER CENT	MEAN MG. %	ST. DEV.	NUM- BER	PER CENT
	19	20	0.14	±0.08	7	7	7	7	0.26	±0.14	19	19	19	19	0.14	±0.08	45	15	0.18	±0.09	103	34
Poor	29	30	0.59	±0.27	30	30	30	30	0.55	±0.22	44	43	44	43	0.45	±0.20	103	34	0.52	±0.22	152	51
Adequate	47	50	0.94	±0.24	66	63	66	63	0.97	±0.26	39	38	39	38	0.92	±0.25	152	51	0.95	±0.25		

June through September. As the plasma vitamin C values tend to lag slightly behind increased consumption of the vitamin when the body is unsaturated, we have divided the year into three arbitrary periods: A—March through June, B—July through October (summer) and C—November through February. There was no seasonal variation in plasma values within groups of mothers with similar diets (Table II). On the other hand, the incidence of certain types of diet was influenced by the seasons. For example, during the summer months (period B) only 7 per cent of the diets were classed as "poor" but during the remainder of the year (periods A and C) the incidence of "poor" diets was 19 and 20 per cent respectively. The incidence of "adequate" diets was the reverse.

Pregnancy.—All agree that the need for vitamin C increases during pregnancy. Some investigators, as we have pointed out, believe that the need becomes progressively greater as pregnancy advances. A study of our data with this point in mind was not entirely satisfactory, chiefly because the major dietary and seasonal fluctuations of plasma vitamin C masked any minor effects which might be due to the progress of pregnancy. The following results from a small group of selected patients suggest that the demands do not increase greatly as pregnancy advances. We found that the dietary intake of vitamin C was fairly constant for each woman during the winter months whether at "poor" or "adequate" levels. Fig. 1 shows that the plasma values of these patients had no downward trend during pregnancy.

Additional evidence was obtained from an analysis of a single dietary class—those with "adequate" diets, during the winter months. Table III shows that the mean plasma value for this group remained about the same throughout pregnancy and delivery. Three patients with very low values probably account for the lower average value obtained during the third trimester. The average value at the time of delivery is again higher, and similar to the values for early pregnancy. From these results we doubt that there is a significant progressively increasing need for vitamin C during pregnancy.

TABLE III. SHOWING VARIATIONS IN PLASMA VITAMIN C IN WOMEN WITH "ADEQUATE" DIETS DURING THE WINTER MONTHS

STAGE OF PREGNANCY	NUMBER	MEAN VALUE MG. %	STANDARD DEVIATION	VALUE FOR "T"*	
First Trimester	8	1.04	± 0.188	0.672	1.72 Not significant
Second Trimester	20	1.03	± 0.263	Not significant	
Third Trimester	15	0.81	± 0.252	2.240	
Delivery	38	0.97	± 0.225	Significant @ 5% level	

*Statistical significance of the difference of the means determined according to Fischer's Table for "t".

Some investigators⁵ have had difficulty in maintaining adequate levels by diet alone. Study of Fig. 1 shows that it was possible to raise the low and intermediate plasma values to a high level and to maintain optimum values at a high level throughout pregnancy by diet alone. This was readily accomplished during the summer months. During the other months it was possible but more difficult.

We found, as did McDevitt et al.,¹⁸ no significant change in plasma vitamin C during labor. Five of eight women examined at the beginning of labor and at delivery showed no change in plasma values; in one an insignificant increase of 0.05 mg. per cent was recorded and in two, decreases of 0.07 and 0.11 mg. per cent respectively.

Sixteen women observed at delivery and again within 24 hours post partum showed a slight tendency toward lower plasma values. Half of these women showed a decrease ranging from 0.14 to 0.25 mg. per cent; the other half showed no significant change in values. These results differ from those obtained for vitamin A in the same patients.¹⁹ Plasma vitamin A *increases* greatly and consistently during the early puerperium.

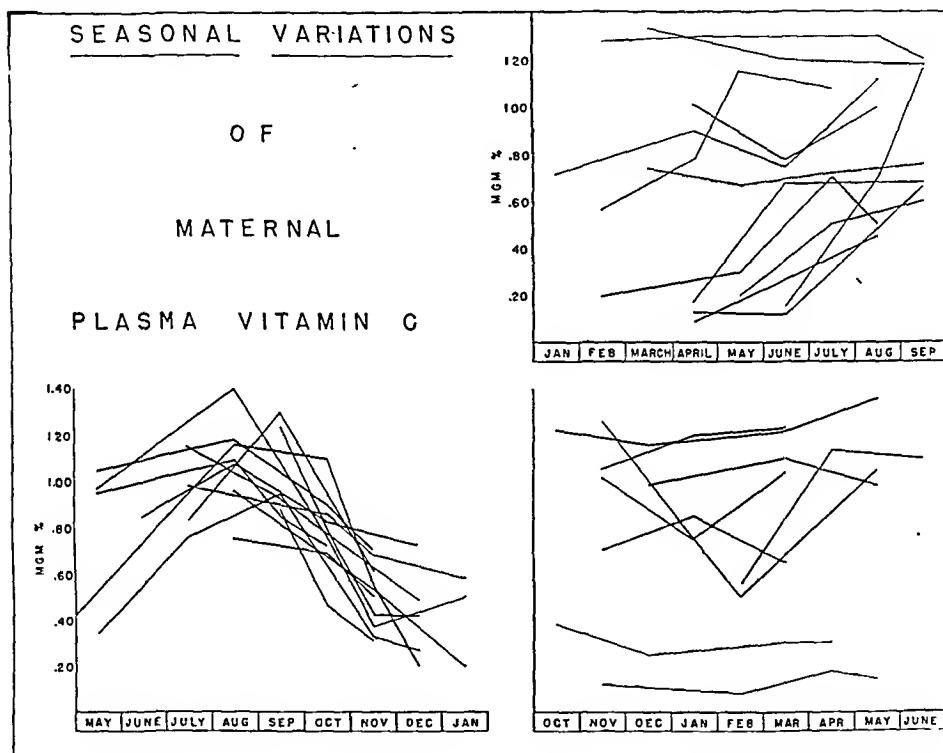


Fig. 1.—Showing seasonal variations in plasma vitamin C throughout each individual pregnancy and delivery. For purposes of greater legibility the group has been divided into three parts according to the season when delivery occurred: Upper right—those delivered during summer; Lower left—those delivered during fall and winter; Lower right—those delivered during spring.

When cesarean section was the method of delivery the early puerperal decrease of vitamin C was more consistent. Five women were observed before and after operation and in each the vitamin decreased from 0.12 to 0.46 mg. per cent.

Complications of Pregnancy.—As might be expected, we found no correlation between plasma levels of vitamin C and such conditions as toxemia of pregnancy, puerperal morbidity, duration of labor and complications of pregnancy in general (data not included). On the other hand, two complications were understandably related to vitamin C deficiency.

The first of these was *hyperemesis gravidarum*. It is unlikely that vitamin C deficiency has to do with the cause of hyperemesis gravidarum, but it can be a serious result. Table IV illustrates the individual plasma values for 11 women with hyperemesis gravidarum. The severity of the emesis, which depends on the duration and frequency of vomiting, is reflected in the plasma value. The woman with the zero value for vitamin C warrants further discussion, as she also had clinical signs of scurvy including the gingival lesions and petechial hemorrhages. These capillary hemorrhages were present not only in the skin but also in the retina. Stander²⁰ reported hemorrhagic retinitis in conjunction with pernicious vomiting of pregnancy in 1932 and advised the interruption of pregnancy when such hemorrhages appeared. We have observed the development and progress of retinal hemorrhages in two patients with severe hyperemesis gravidarum. Both women had clinical signs of scurvy. One had no vitamin C in the plasma; unfortunately the other was not studied by laboratory methods. In each instance fresh retinal hemorrhages continued to appear as long as vitamin C was withheld. Administration of vitamin K was without effect on the retina. However, the intravenous injection of 500 mg. of ascorbic acid daily stopped the development of new hemorrhages within 48 hours, and forthwith the retina returned to normal. In neither instance was therapeutic abortion necessary. It must be understood that the administration of vitamin C was but one of the many necessary therapeutic measures.

TABLE IV. PLASMA VITAMIN C VALUES IN HYPEREMESIS GRAVIDARUM

PATIENT	SEVERITY OF VOMITING	PLASMA VITAMIN C MG. %
Bl.	Mild	0.87
Bu.	Mild	0.63
Du.	Mild	0.59
Wa.	Mild	0.28
We.	Mild	0.38
Ga.	Moderate	0.09
Ka.	Moderate	0.22
Pr.	Moderate	0.17
Pru.	Moderate	0.28
He.	Severe	0.08
We.	Severe	0.00

A careful survey of our data failed to demonstrate any correlation between the plasma vitamin C values and the amount of post-partum bleeding, although on rare occasions a deficiency of vitamin C may be responsible for *post-partum hemorrhage*. Fifty-one women with less than 200 c.c. blood loss at the time of delivery had an average plasma vitamin C value of 0.70 mg. per cent while for 42 women with a blood loss between 200 and 400 c.c., the figure was 0.73 mg. per cent. Five women had post-partum hemorrhage—blood loss in excess of 400 c.c. Four of the five had "normal" value for plasma vitamin C but one had a zero value. A careful study of this patient revealed no other possible cause for the bleeding such as uterine inertia, retained secundines or laceration of the genital tract. For these reasons we believe the bleeding in this one instance was due to vitamin C deficiency.

Fetal-Maternal Relationships

The fetal plasma vitamin C values always exceeded those of the mother at the time of delivery. There were no exceptions under ordinary circumstances, and only a single exception was noted under experimental conditions to be described later in this paper. Ninety-four women and their babies were studied. The maternal values averaged 0.68 mg. per cent (standard deviation ± 0.39), and the infants' averaged 1.32 (standard deviation ± 0.48). On the basis of these figures it would appear that the fetal vitamin C level is about twice that of the mother, but average values in this instance are misleading. Further study of individual pairs showed that the maternal-fetal ratio of 1:2 was not always maintained (Fig. 2). This graph was made by plotting the value for each mother against that of her infant. Superimposed is a fitted curve which expresses the average change in maternal-fetal relationship which occurs at various levels of vitamin C concentration. For example, fetal values may be five to eight times greater than maternal values when the latter are low; when maternal values are high the fetal values may be but a half time higher. The shape of the curve (Fig. 2) suggests that at some high level both maternal and fetal values might be equal. To test this possibility we made the following observations.

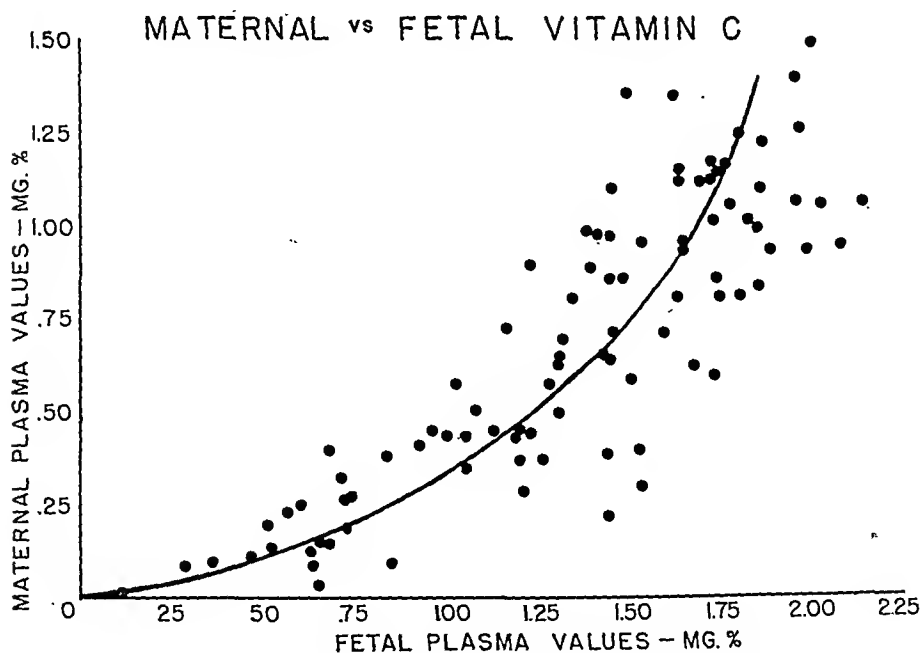


Fig. 2.—Individual maternal and fetal values at the time of delivery, with superimposed fitted curve.

We found intravenous injection of ascorbic acid to be the most satisfactory method of elevating maternal blood values during labor. Oral administration was unsatisfactory because of the derangements of digestion which usually accompany labor. Ascorbic acid in doses of 100,

250 and 500 mg. were given intravenously to women in labor. First the maternal values were determined. Then the vitamin was injected. Following this, periods of time ranging from 20 minutes to 15 hours elapsed before delivery. At the time of delivery both maternal and fetal values were determined. Table V details the results. It is evi-

TABLE V. SHOWING THE EFFECT OF INTRAVENOUSLY ADMINISTERED ASCORBIC ACID ON MATERNAL AND FETAL PLASMA VITAMIN C LEVELS—MG. PER CENT

PATIENT	DOSE MG.	TIME BETWEEN INJECTION AND DELIVERY (HOURS)	MOTHER'S LEVEL BEFORE INJECTION	MOTHER'S LEVEL AT DELIVERY	INFANT'S LEVEL AT DELIVERY	DIFFER- ENCE OF MATERNAL VALUES	DIFFER- ENCE BETWEEN MOTHER AND BABY AT TIME OF DELIVERY
Ad.	0*	½	0.61	0.57	1.32	-0.04	+0.65
Co.	100	¼	0.30	0.52	0.96	+0.22	+0.44
Hal.	100	¾	0.34	1.26	2.16	+0.42	+0.90
Har.	250	¼	0.65	1.83	1.62	+1.18	-0.21
Ke.	250	1½	1.42	2.04	2.14	+0.62	+0.10
La.	250	8	0.76	1.23	1.70	+0.47	+0.47
Lu.	500	½	1.04	2.49	2.44	+1.45	-0.05
Man.	500	1	0.72	2.11	2.26	+1.39	+0.15
Ma.	500	1¼	0.40	1.62	1.64	+1.22	+0.02
Pe.	500	2	1.10	1.90	2.29	+0.80	+0.39
Pl.	500	2½	0.73	1.65	2.06	+0.92	+0.41
Re.	500	5½	0.70	1.40	2.42	+0.70	+1.02
Su.	500	6	1.28	1.96	2.40	+0.68	+0.44
Wa.	500	12	0.98	1.18	2.46	+0.20	+1.28
Wi.	500	15	1.09	1.30	1.75	+0.21	+0.45

*Control injection of saline solution.

dent that both maternal and fetal values can be increased by intravenous vitamin C. Fetal values increased more slowly and did not reach an equilibrium with maternal values until approximately one to one and one-half hours after injection. When the time interval between the injection and delivery exceeded two hours the maternal values had begun to decline but the fetal level was maintained and values remained high for at least 12 hours.

Discussion

All of us who live in the northern latitude of the United States are well aware of the seasonal variations in foodstuffs rich in ascorbic acid. Many of these foods are difficult to obtain in the winter time, especially in the rural communities. Furthermore, when these foods are available, much potency may be lost by aging, processing, and exposure to air before serving. These several factors, we believe, were largely responsible for the seasonal changes noted in our results. The frequency of "poor" diets with their attendant low plasma vitamin C levels (mean value 0.18 mg. per cent) increased from 7 per cent during the summer months to 20 per cent during the other months. Nevertheless, and in spite of these seasonal factors, it was possible to maintain an optimal plasma vitamin C level during the winter months. It was

also possible to maintain a high level throughout pregnancy and delivery by means of diet alone. Thirteen of thirty-three women who received adequate diets had plasma values above 1.00 mg. per cent at the time of delivery. This is contrary to the findings of Teel et al.⁵ These investigators also reported declining values during pregnancy in spite of attempts to improve the diet. Our results were otherwise for we could maintain high values and elevate others by diet alone. The liberal ingestion of citrus fruits was an important factor in maintaining the high plasma values of our patients. Unquestionably the generous consumption of citrus fruits is a most satisfactory method of providing adequate amounts of vitamin C and they should be obtained every day during pregnancy. In this connection it should be pointed out that we observed little benefit from the administration of small supplements (25 mg.) of ascorbic acid. This additional amount of the vitamin did not alter plasma levels when given to women with good diets and it was far too little to supply the needs of women with inadequate diets. The use of such small supplements might give the physician a false sense of security as far as vitamin C metabolism is concerned.

There can be no doubt about the increased need for vitamin C during pregnancy, although we made no attempt to confirm experimentally this generally accepted statement. We could not show that the requirements for vitamin C increase progressively during pregnancy. If there is such an increasing need it cannot be great, and can easily be masked by the seasonal variations. For example (Fig. 1) if all our observations had begun in late winter and terminated in midsummer they would have suggested that plasma values *increased* with the progress of pregnancy. If, on the other hand, they had begun in summer and terminated in winter the opposite opinion would have been formed. During the winter the intake of vitamin C of our patients was fairly stable as were the plasma values and there was no tendency toward decreased values as pregnancy progressed.

Plasma vitamin C did not change significantly during the course of ordinary labor. While we did not observe the results following unusually long or difficult labors, it is not unlikely that vitamin C might be reduced under such conditions. There were no unusual changes during the early puerperium, although there was a slight tendency towards lowered values. This is in contrast to the behavior of plasma vitamin A, previously reported by us, which increases uniformly and significantly during the first 24 hours after delivery. Following cesarean section plasma vitamin C decreased consistently; a result not unexpected and readily explained by the nature of the procedure.

A deficiency of vitamin C may be one of several serious consequences of hyperemesis gravidarum. A reduction in plasma values was noted after mild vomiting and the decrease progressed with the severity and duration of the emesis. As far as we know vitamin C plays no part

in the cause of the disease, but the development of subclinical or clinical scurvy can be a disturbing and dangerous additional complication. Retinal hemorrhages, which are known to be a grave prognostic sign, are apparently a manifestation of generalized capillary fragility, and in that respect are similar to the petechiae of the skin. The appearance and development of retinal hemorrhages was not changed until ample amounts of ascorbic acid had been given (1,000 mg.). It is true that these hemorrhages are a grave prognostic sign, but they alone should not necessarily be used as an indication for therapeutic abortion. They are merely a sign of grave vitamin C deficiency. It is necessary to warn that administration of vitamin C is but one of many important therapeutic measures necessary for successful treatment of hyperemesis gravidarum.

We could show no relationship between plasma vitamin C and the ordinary amounts of blood loss after delivery. Many factors, some of them unknown, govern the amount of blood loss, and it would be exceedingly difficult to discover the influence of vitamin C should it exist. The situation as regards post-partum hemorrhage is similar. There are many etiologic factors. In one instance, however, we believe that a vitamin C deficiency (plasma value 0) was responsible for post-partum hemorrhage, as no other cause for the bleeding could be found.

Maternal-Fetal Relationship

When maternal requirements for vitamin C are not met during pregnancy the mother becomes depleted at the expense of the fetus. This is shown in Fig. 2. For example, only seven of 94 babies had plasma values below 0.60 mg. per cent while nearly half (41) of the mothers had values below that level. Never under ordinary fasting conditions did we observe a mother whose plasma vitamin C equalled that of her newborn infant. With one exception maternal values did not go above 1.40 mg. per cent but approximately 50 per cent of the fetal values were from 1.50 to 2.00 mg. per cent. Only 21 per cent of the infants' values were below 1.00 mg. per cent. Thus we see that about 80 per cent of the newborn infants usually have a normal complement of vitamin C. Nevertheless this does not permit the clinician to casually disregard the future state of the infant, for it has been shown that fetal values diminish rapidly after birth¹¹ and the sole natural source of vitamin C at this time is from the milk.

What is the mechanism by which fetal blood levels are kept higher than the mothers'? Synthesis of ascorbic acid by the fetus could explain the discrepancy. However, there is no convincing evidence that man, infants, placental or other animal tissue can synthesize ascorbic acid.²¹ Exclusive of synthesis the remaining source is the mother. Needham²² has said that most low molecular weight crystalline substances pass readily through the placenta and equal concentrations usually are reached in both bloods. Obviously such is not the ordinary

state of affairs for ascorbic acid. Though it passes readily from mother to fetus, as we have shown, an equilibrium is not maintained.

Manahan and Eastman,⁴ and McDevitt et al.¹⁸ suggest that a mechanism of selective filtration is responsible. This is a possible explanation for the passage of crystalline substances from a dilute into a more concentrated solution, though definite proof is still lacking.

From our studies of parenteral administration of ascorbic acid we have developed the following hypothesis: We know that ingestion or parenteral administration of natural or synthetic vitamin C results in a temporary elevation of the plasma values, which in most adults returns to fasting level within four hours. Our results showed that parenteral administration of vitamin C elevated maternal and fetal values to an equal level. Our studies further showed that the period of equilibrium between maternal and fetal values was short. There followed a rapid reduction of maternal values to normal while the fetal values remained high. This suggests to us that the placenta is a barrier to the re-entrance of ascorbic acid from the fetal into the maternal circulation. Maternal values continue to fall, presumably due to utilization, excretion and a small amount of storage. The fetus, however, has no method of excretion save through the placenta, and fetal values remain high because of *selective retention* of the placenta. Only after the fetus has utilized circulating vitamin C does the blood level drop, and at this time additional amounts may be obtained from the maternal circulation, in the manner just described. This mechanism of selective retention would account for the differences between maternal and fetal values throughout all ranges, as well as the dependence of the fetus on the mother for the vitamin.

Summary and Conclusions

Forty-six mothers had repeated determinations of plasma vitamin C during the course of pregnancy. One hundred and fifty-one mothers were observed once or twice during pregnancy, and 110 of these mothers and their infants were observed at the time of delivery. Over 500 photolorimetric determinations of plasma vitamin C were done. From these observations we have concluded that:

1. The plasma vitamin C level reflects the dietary intake of this substance. The mean plasma value for mothers with an adequate diet was 0.95 mg. per cent, with a fair diet, 0.52 mg. per cent and with a poor diet, 0.18 mg. per cent.

2. Season exerts a marked influence. During the summer months diets poor in vitamin C were uncommon (7%), while at the same time most (64%) of the mothers received an adequate diet. During the remainder of the year 20 per cent had poor diets and 43 per cent had adequate diets.

3. Optimal plasma values can be maintained by diet alone as long as it contains liberal amounts of foods rich in vitamin C. Fresh citrus

fruits, tomatoes and berries are excellent sources of ascorbic acid, and at least one of this group of fruits should be eaten each day during pregnancy.

4. Small doses of ascorbic acid, e.g., 25 mg. daily, are of little benefit alone, and they may lead the physician into a false sense of security unless he realizes that the daily requirements of the pregnant woman are *much* greater. If the woman receives an *adequate diet* there is no need for synthetic ascorbic acid. By adding it routinely to an adequate diet the physician may waste a valuable drug which is needed elsewhere during wartimes.

5. Blood levels of vitamin C did not change during labor. They tended to be slightly lower during the early puerperium and were definitely but not alarmingly lower after delivery by cesarean section.

6. Hyperemesis gravidarum may lead to dangerously low levels of vitamin C. Clinical scurvy may appear. The retinal hemorrhages of severe hyperemesis gravidarum are a manifestation of vitamin C deficiency and are similar to petechial hemorrhages seen elsewhere. These hemorrhages cease after adequate therapy with vitamin C, henceforth they are not necessarily an indication for the use of therapeutic abortion.

7. On rare occasions a deficiency of vitamin C may lead to postpartum hemorrhage, but the plasma values in general are not related to ordinary blood loss following delivery.

8. The fetus receives its supply of vitamin C at the expense of the mother and, under fasting conditions the fetal values are always higher than those of the mother, the difference being relatively greatest when maternal values are low.

9. Fetal blood vitamin C may be maintained at a level higher than the mother's by a process of selective retention by the placenta.

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LOW-DOSAGE IRRADIATION IN THE TREATMENT OF AMENORRHEA*

An Analysis of an Additional Ninety-Two Cases

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OUR three previous reports¹ included a total of two hundred and thirty-eight patients treated exclusively by means of low-dosage roentgen irradiation of the pituitary gland and ovaries for the relief of functional menstrual disorders. A long-term follow-up of one hundred and thirty-six of these patients was recently concluded by Reidenberg,² who found that 71 per cent of the amenorrheal and 78 per cent of the oligomenorrheal patients, treated between 1927 and 1937, are still menstruating at normal intervals. His long-term survey also disclosed that the eighty children born to some of these women are physically and mentally normal. Some of these children are now of high-school age. He found, moreover, that the three children of a woman who had received three courses of treatment at lengthy intervals are likewise physically and mentally normal. It is, therefore, reasonable to assume that low-dosage irradiation of the ovaries has no deleterious effect on the offspring of the first generation.

The erroneous concept that x-rays, regardless of the smallness of the dose, invariably cause structural and, consequently, functional deterioration of human cells is responsible for the reluctance of the profession to employ one of the most valuable agents in the treatment of amenorrhea. The published clinical results of many gynecologists and radiologists³ refute this belief.

That subminimal doses of roentgen rays, such as are employed in diagnostic procedures, do not injure even the sensitive ovarian cells of infants is clinically established. Such damage to the ovarian cells of infants was neither anticipated nor observed clinically even with the use of the old type of apparatus which required approximately five times the amount of irradiation, because of the absence of screens. That the cells of the mature ovary are more resistant to irradiation is well known. The problem is, therefore, purely a question of dosage in relation to the sensitiveness of the tissues exposed to the roentgen rays.

It seemed interesting to determine how many tissue roentgens are delivered at a depth of 7 cm. (the usual distance of the ovaries from the surface in a woman of normal weight) in a complete study of the urinary tract which often requires eight to twelve films.

*Read at a meeting of the Philadelphia Obstetrical Society, May 6, 1943.

J. L. Weatherwax, x-ray physicist, kindly volunteered the information. He states: "For 70 kv., 30 Ma. at 25 in. from the x-ray film and 17.5 in. from the skin of the patient, 4.2 roentgens were delivered to the skin of the patient; while approximately 0.6 tissue roentgens were delivered at a depth of 7 cm. for each film taken. These measurements were made in a water phantom with a nonshockproof x-ray tube and 1 mm. Al. filter at a distance of 50 cm. (20 in.) and gives approximately 15 per cent radiation reaching a depth of 7 cm. Your x-ray tube has approximately $\frac{1}{2}$ mm. Al. inherent and $\frac{1}{2}$ mm. Al. on the outside, which makes a total of 1 mm. Al. filter."

Twelve films would deliver 50.4 roentgens to skin or 7.2 tissue roentgens to the ovaries. The opponents of low-dosage irradiation concede that 7.2 tissue roentgens are harmless but fail to furnish proof that 32.5 tissue roentgens, delivered by the Edeiken technique, produce either structural or functional regressive changes in the human ovary.

In the light of clinical and experimental observations on low-dosage irradiation, the independence of functional from indiscernible structural changes in the cell must be conceived. We must envisage a dose of roentgen rays too small to produce even microscopic changes in the cell, yet capable of modifying its functional activity, possibly through indiscernible changes, such as rearrangement of electrons, etc.

For instance, in thirty-eight young women for whom panhysterectomies were planned because of early carcinoma of the cervix, Wagner and Schoenhof⁴ administered 5 to 10 per cent of a skin erythema dose of x-rays to one ovary of each patient several weeks before operation. In each instance, the histologic picture in the irradiated ovary revealed no evidence of degenerative changes as a result of the low-dosage irradiation. In fact, there were more follicles of equal maturity in the irradiated ovary than in the nonirradiated one.

Of the numerous statistical reports³ in the literature on the clinical effects of low-dosage irradiation of the pituitary gland and ovaries, not one is unfavorable. All of them indicate a degree of success not obtainable with any other single agent or combination of agents in the treatment of functional menstrual disorders and the frequently associated infertility. Nevertheless, many gynecologists and radiologists, who have never applied this treatment, solemnly warn the profession against its use—purely on the basis of their experience with large doses of roentgen rays for the relief of conditions unrelated to amenorrhea.

It is not the premise of this presentation to discuss the problem on the basis of theory or animal experimentation, but rather to record observations on the use of this measure in a group of ninety-two patients not included in our several previous reports.

Selection of the Clinical Material

Only those patients who were physically well, as shown by clinical and laboratory studies, were subjected to low-dosage irradiation of the pituitary gland and ovaries. Those suffering from hypo- or hyperthyroidism or from pituitary adenomas naturally were not given this

treatment. Girls under seventeen and women over thirty-nine years of age were excluded, because their ovaries are either immature and, therefore, too sensitive to irradiation or in the phase of natural decline. Thirteen of the patients were between seventeen and twenty years of age; seventy-one ranged in age between twenty-one and thirty; and only eight were between thirty and thirty-six. The possible presence of pregnancy was eliminated by a biologic test, unless the patient happened to have recently menstruated.

Cured patients who had received simultaneously with the x-ray treatment some form of organotherapy are deliberately excluded from this study on the assumption that the latter may have contributed to the good results. On the other hand, patients who failed to respond to combined roentgen-ray and endocrine therapy are included in the failures because of our conviction that the endocrine products were not responsible for the lack of response to irradiation. Those who failed to respond within two months after irradiation or conceived soon after treatment without subsequent restoration of the menstrual rhythm, are also excluded from the list of cures in the belief that the pregnancies were incidental and, therefore, not attributable to the irradiation. All patients were followed up for a period of one or more years. Instances of improvement or restoration of the menstrual function for a period of less than a year are grouped as failures. Adherence to these rigid requirements, set up as a guard against erroneous deductions, justifies the presentation of this report.

Technique of Low-Dosage Irradiation

The ninety-two patients were treated by several radiologists who employed for years the technique of Edeiken⁵ with uniformly good results. The technique may be described as follows: 135 kv., 5 Ma. at a distance of 35 cm., with $\frac{1}{4}$ mm. cu. and 1 mm. of aluminum filtration through an anterior pelvic field. Depending on the size of the pelvis and the thickness of the abdominal wall, a dose of 50 to 90 r. measured in air is given. This is repeated three times at intervals of one week. The pituitary gland is treated with the same dosage at the same time through a field of 5 by 5 cm. just above and posterior to the midpoint of a line joining the outer canthus of the eye and the external auditory meatus. Close adherence to this technique or to the one employed by Kaplan⁶ avoids ill effects. Variation in dosage and method of application is, to say the least, confusing in so far as determination of results are concerned.

Results of Treatment

Ten of the ninety-two patients had not menstruated for periods varying from sixteen months to six years, with an average of two years and eight months for the group. Five of them (50 per cent), including the one with total amenorrhea for six years, have been menstruating regularly during a follow-up period varying from one to five years, with an average of three years for the group. Twelve of the ninety-two patients had menstruated at intervals of six months. Eight of these twelve (66 per cent) have been menstruating normally during a follow-up period averaging two and a half years. Sixty-eight of the ninety-two patients had a milder type of amenorrhea, known as oligomenorrhea, having menstruated before treatment at intervals of from two to four months. Fifty-two of these sixty-eight (76.5 per cent) have been

menstruating normally during a follow-up period ranging from one to five years, with an average of two years and seven months for the entire group.

One of the patients, aged eighteen years, who had never menstruated, despite intensive organotherapy, responded promptly to low-dosage irradiation. Previous experience has shown, however, that primary amenorrhea does not, as a rule, respond to this type of treatment, probably because of an inherent Müllerian defect. It was employed in this case as a last resort. Another patient, aged twenty-two years, was supposedly adversely affected by the treatment. She had been completely amenorrheic for eight months despite the daily administration of 3 grains of desiccated thyroid substance to maintain a normal basal metabolic rate. Her thyroid gland was not enlarged and she lacked the usual symptoms and signs of hypothyroidism. Low-dosage irradiation was tried in June, 1942, without relief. She has remained totally amenorrheic since then. It is obvious that the treatment was ill chosen, for she apparently has a thyroid malfunction secondary to a rare type of pituitary deficiency wherein thyroid substances as well as low-dosage irradiation are ineffective.

A second course of treatment was administered to ten of the ninety-two patients, who had shown improvement in menstrual rhythm following the first course. Only three of ten were thereby restored to normal menstrual periodicity. The remaining seven patients were, however, not adversely affected by it. One patient, previously mentioned, who had received three courses of treatment at lengthy intervals, has delivered three healthy children and is still menstruating normally.

This study bears out our previous observations that the percentage of cures is inversely proportional to the severity of the amenorrhea. Thus, those who had menstruated at intervals of two to four months yielded the highest number of cures (76.5 per cent); those who had menstruated at intervals of six months yielded 66 per cent cures; whereas those who had not menstruated at all for sixteen months to five years prior to treatment yielded only 50 per cent cures.

Influence of Low-Dosage Irradiation on Associated Conditions

Of the ninety-two amenorrheic women, seventeen had also experienced episodes of prolonged uterine bleeding following variable periods of amenorrhea. Control of the bleeding was the more important consideration. It was accomplished in twelve of the seventeen by means of injections of chorionic gonadotropin in doses of 500 international units daily as long as the bleeding persisted. This hormone is known to have no stimulating effect on the human ovary. It does, however, through some unknown means, arrest dysfunctional uterine bleeding in most women of childbearing age, but does not restore the menstrual rhythm. All of the seventeen patients were subsequently subjected to low-dosage irradiation but in only six of the seventeen was the menstrual rhythm restored.

Sterility was an associated and important factor in fifty-four of the ninety-two patients. They were involuntarily barren for two to fourteen years, with an average of three years for the entire group. In most of them, other than endocrine factors, such as nonpatency of the Fallopian tubes, coexisted and were simultaneously treated. Thirty of the fifty-four infertile women conceived at variable intervals after termination of treatment. Twenty-eight of them delivered healthy in-

phants; the remaining two aborted during the first trimester of pregnancy. Twenty-one of these thirty patients conceived within four months after termination of low-dosage irradiation—a few without an intervening menstrual flow. Complete restoration of the menstrual cycle for over a year in nineteen of the twenty-one women who conceived soon after treatment implies that conception was the result of improved ovarian activity. Two of the 28 successful pregnancies followed a second course of low-dosage irradiation, given because the first attempt failed to restore completely the menstrual function.

Summary

A follow-up for nearly three years of ninety-two additional cases of amenorrhea, treated by means of low-dosage irradiation of the pituitary gland and ovaries, shows that sixty-five (seventy-two per cent) of the patients have been menstruating normally. It is noted that the data gathered from a long-term follow-up of one hundred and sixty-five cases, similarly treated and previously reported, show permanency of the cures and the safety of the procedure to both the patient and her offspring.

Of the ninety-two amenorrheic patients in the present group, fifty-four desired offspring but had not conceived despite the intensive use of organotherapy and other measures for several years. Twenty-eight (fifty-four per cent) of the fifty-four barren women conceived and carried to term healthy infants; two aborted during the first trimester of pregnancy. All of the thirty women have been menstruating normally since the termination of pregnancy.

Low-dosage irradiation of the pituitary gland and ovaries for the relief of amenorrhea should not be administered without a preliminary pelvic examination and a dependable biologic pregnancy test, unless the patient happened to have menstruated a couple of weeks previously.

A survey of the literature on low-dosage irradiation of the pituitary gland and ovaries, as employed for the relief of amenorrhea, reveals no adverse effects either on the patients or their offspring. Instances of harm recorded in the literature were the result of heavy irradiation, employed in the treatment of uterine fibroids and kindred conditions.

The importance of employing a uniform technique and dosage is emphasized, for the boundary line between the clinically effective and the injurious dose of roentgen rays has not been determined.

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Discussion

DR. JACOB HOFFMAN.—I should like to emphasize that it is still debatable whether small doses of the x-rays are capable of stimulating endocrine function. Even if this were granted, there is nothing to suggest that, when applied to the pituitary gland, the rays will affect only its gonadotropic activity and leave unaltered all the other important functions now ascribed to this gland. Fortunately, this structure would appear to be fairly resistant to the action of the x-rays and the danger of damage is not serious. This is apparently not true of the ovary. While ovarian function may remain undisturbed after irradiation in some women, in others permanent damage may result from the application of comparatively small doses. I have encountered women who became permanently amenorrheic and sterile following such treatment. It must be borne in mind that, in the treatment of "dysfunctional menstrual disorders," we are dealing with sub-normally functioning ovaries which may be further depressed by a dose of x-ray which might leave the normal ovary unharmed.

Though a return to normal menstrual rhythmicity and fertility may not infrequently be observed after low-dosage irradiation, we are not justified in crediting the rays with these results, for other measures which may have a curative effect are usually also employed in such cases. In the sterile woman, for example, curettage and tubal insufflation are performed for diagnostic purposes. Curettage alone is known to be followed by conception in from 20 to 25 per cent of the cases, while from 15 to 18 per cent may benefit from tubal insufflation. In the treatment of menstrual disorders, spontaneous correction of the underlying deficiency may account for a goodly number of the cures ascribed to irradiation. It is noteworthy that most of the cases showing a favorable response are younger women, whose condition is often self-limited.

DR. ARTHUR FIRST.—Dr. Mazer has given us convincing proof to justify his extreme optimism in regard to the use of low dosage irradiation of the pituitary gland and ovaries in the treatment of amenorrhea. This is the fourth report that he has submitted, making a total of 330 patients treated and followed up in almost two decades. This is certainly a large enough group of cases to give weight to Dr. Mazer's conclusions of the harmlessness of the method and the high percentage of cures.

My role in discussing this paper is simply to substantiate Dr. Mazer's claims from my own experience in private work with in addition the use of this method for the past fifteen years in the Sterility Clinic of Jefferson. Although we have a smaller series of patients, our results have been equally as good.

There are, however, still a number of "die-hards" who refuse to countenance this form of treatment and who still cry out against it. In the 1942 Year Book of Obstetrics and Gynecology, Greenhill makes an editorial comment, "I should like to repeat my annual warning that until we know much more about the late effects of irradiation treatment, we should be extremely careful about employing it in young women either for amenorrhea or for sterility." Traut of New York City at a recent meeting of the Texas Association of Obstetricians and Gynecologists stated, "such experiments, for such they are, are inadequately controlled so that one cannot state with any degree of assurance that the radiation therapy was of substantial benefit. Experimental work which has been done on mice and guinea pigs demonstrates beyond a doubt that in these animals the effect of radiation may be transmitted and appear two, three, or even four generations later in the form of abnormal developments of the extremities resulting in partial or complete absence of arms or legs or with clubbed feet."

For many years I have made a study of the large number of sterility patients who abort within a few months after getting pregnant and of the not too infrequent patient who after a great deal of endocrine therapy goes to term but

delivers an abnormal fetus, evidence of so-called low reproductive efficiency or poor germ plasm. Would it not be most illogical to refuse to treat sterility patients because of these remote possibilities? The large number of sterile women who are ultimately delivered of healthy children warrants trying all the means at our command to cure them. By the same analogy one is not justified in fearing to try low-dosage irradiation since a higher percentage of blighted ova is to be expected in these women regardless of the type of therapy employed.

I would like to cite an interesting case of a private patient, Mrs. F. M., who had been sterile for thirteen years, with variable periods of amenorrhea of from three to five months. In May, 1942, she received a complete x-ray study of her gall bladder, gastrointestinal tract, and spine. Following this study she had two normal periods spaced one month apart for the first time in years and then promptly became pregnant and delivered a healthy baby at term. The roentgenologist informs me that this patient inadvertently received almost as much stimulation to her ovaries as she would have received in low-dosage irradiation. It is interesting to conjecture whether this x-ray investigation cured her amenorrhea and accounted for the cure of her long-standing sterility.

Dr. Mazer is to be congratulated for the intensive follow-up study of his patients to prove that at present low-dosage irradiation yields better results than any form of organotherapy in the treatment of amenorrhea. Whether endocrine therapy will eventually give as good results as low-dosage x-ray remains to be seen.

DR. S. LEON ISRAEL.—We have all had the experience of having a patient who had been referred for x-ray treatment return to us with what appeared to be an adverse effect. If one inquires closely, he usually finds that the radiologist has administered a dose larger than the one recommended. In Dr. Mazer's earlier papers, as well as in the one by the essayists tonight, the importance of not varying the dosage is well stressed. Dr. Ira I. Kaplan of New York has a similar series of patients with equally favorable results. He also stresses the point of never exceeding the maximum dose recommended for this form of therapy.

The problem of tissue harm following such low-dosage irradiation is a purely imaginary one. With such dosage, no one has ever demonstrated destruction of ovarian tissue. It is, however, very easy to prove that no harm occurs. About three years ago, Dr. Philip J. Hodes and I experimented with 125 isolated rabbits. The animals were treated with x-rays to the pituitary and ovarian regions, employing a dose similar to that employed in the human being for low-dosage purposes. In several animals, the same dose was administered. We could not detect any histologic change in the ovaries of the treated animals. Moreover, in each instance, the animal's ovaries, following irradiation, responded to pregnancy urine injections or to mating with the usual ovulation points. At least in the rabbit, such irradiation does no obvious harm.

DR. CHARLES MAZER.—Concerning Dr. Hoffman's remarks, be it remembered that it was not the premise of this presentation to discuss the problem on the basis of theory or animal experimentation. This paper is confined to clinical observations. Moreover, if Dr. Hoffman's clinical experience with low-dosage irradiation of the pituitary gland and ovaries during the past fifteen years has been as bad as he states, why has he not reported this fact? Thus far, not one of the numerous reports in the literature has been unfavorable.

THE USE OF THE HYPNOIDAL STATE AS AN AMNESIC, ANALGESIC AND ANESTHETIC AGENT IN OBSTETRICS

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THE late Dr. J. B. DeLee,¹ whose encouragement stimulated our research in this field has stated that, "the only anesthetic that is without danger is hypnotism. Psychiatrists claim no person ever died under pure hypnosis. This mental narcotic was introduced into surgery by Recamier in 1821 and obstetricians have dallied a little with it. Von Oettingen in 1921, discouraged by the bad experience of twilight sleep tried it systematically, others tried posthypnotic suggestion which means putting the gravida in a trance and suggesting a painless labor at term. While I have not used pure hypnotism very often, I have used suggestion a great deal, indeed almost constantly and I am irked when I see how my colleagues neglect to avail themselves of this harmless and potent remedy."

The relief of pain in childbirth has been one of the long sought goals of the medical profession. We believe the only method that has complete safety for mother and baby, without altering the normal mechanism of labor, is hypnosis. We maintain that hypnosis has unrealized possibilities for making childbirth not simply the equivalent of a surgical operation, but rather a satisfying psychological experience which may fulfill deeply felt and sometimes unrecognized and unformulated needs of the mother. This rational method of analgesia and anesthesia receives a brief but favorable paragraph in the textbook on obstetrics by DeLee and Greenhill,² who state that, "hypnosis has been used for a long time in obstetrics and should be employed more often than it is at present. Even if complete hypnosis is not to be resorted to, physicians should remember that repeated suggestions with or without the aid of medication can accomplish a great deal in labor, particularly for the relief of fear as well as the pains of labor."

From Germany and Russia, numerous cases of painless childbirth are reported as having taken place by the use of preconfinement and labor suggestions given under hypnosis, either in its pure form or super induced by small amounts of opiates: Kirstein,³ Heberer,⁴ Von Oettingen,⁵ Hartmann,⁶ Franke,⁷ Schultze-Rhonhof,⁸ Kogerer,⁹ Falk,¹⁰ Friedlander.¹¹

From published reports it seems that this was a popular method of delivery at the Heidelberg clinic.³ Wolff¹⁴ has confirmed the practical usefulness of this method and through the medium of narcotics and hypnosis succeeded in inducing analgesia and anesthesia in suitable patients.

We have modified these methods by the induction of amnesia, analgesia and anesthesia early in labor, thus eliminating all pain and discomfort continuously for the parturient until the completion of labor and perineal repair. In most of our cases pure hypnosis was used.

Since 1931, one of us (W. S. K.) has successfully managed the entire course of eleven out of twelve confinements with this method. There was only one failure in this small series of cases. Ten of our patients were primiparas and one was a multipara, the latter was delivered twice under hypnosis. Prophylactic forceps, episiotomy, and perineorrhaphy were performed in all of our cases.

The technique of hypnotism has been ably described by Erickson,¹⁵ Bramwell,¹⁶ Schilder and Kauders,¹⁷ and others.

The various stages of hypnosis have been thoroughly described by Young,¹⁸ Erickson,¹⁹ and many others. The former has reviewed the world literature up to 1931.

Management of the Prenatal Period

The patient is placed in a deep hypnotic state before the seventh month of gestation. Posthypnotic suggestions are given to the effect that her labor will be entirely painless, that she will have no recollection of the entire procedure, and that she will look forward to her confinement with a feeling of joy and happiness instead of dread and anticipation. Posthypnotic suggestions last about a month, and when repeated often enough the effect will become permanent.^{20, 21} The nature and character of these posthypnotic suggestions have been described by Erickson²² as separate hypnotic states arising spontaneously in the individual. The gravida is then conditioned to the voice of the operator. Suggestions are given that she will fall into a deep hypnotic sleep at a given command. In addition, she is told she will follow all suggestions given her during this period.

The patient returns every two weeks and the same suggestions are repeated to her in the hypnotic trance, which is a state of increased hypersuggestibility. The percentage of individuals that can be hypnotized, and the depth of hypnosis varies with the experience and ability of the operator. In our experience, comprising several thousand cases of hypnosis, the incidence of success has been about 90 per cent. Forel, Wetterstrand and others report similar results. In addition, the various combinations of suggestive therapy were utilized successfully in several of our patients to create an aversion to food, tobacco and alcohol. A conditioned reflex technique described by one of us (W. S. K.)²³ was used. Also, the multiplicity of various complaints, i.e., aches, pains, heartburn and constipation were relieved with remarkable ease.

It is imperative that the gravida maintain complete confidence and rapport with the operator. Suggestions must be dignified at all times

and in keeping with the gravida's desires. After the proper training or conditioning the gravida can be put into an amnesic, analgesic and anesthetic state in five or ten seconds.

Management During Labor and Delivery

Hypnotic sleep is induced when the gravida is in active labor, or when the cervix is dilated between two to four centimeters. The patient is told that her sleep will be deep and continuous. Also, she will hear only the commands of the operator or the person placed in rapport with her.

Our experience has been that these patients, after careful preparation, will be most cooperative during labor. They can converse with the operator, and ask for food, urinate or defecate at their own request. They lie motionless and require no particular attention except routine care. The normal mechanism of labor is not interfered with and during the latter part of the second stage the gravida can be told to bear down with each contraction, thereby facilitating the completion of the expulsive stage.

The respiration is diaphragmatic in type, the pupils are usually fixed and dilated. The limbs can be made cataleptic or flaccid during delivery and complete relaxation of the entire body can be produced simply by command. Any type of operative delivery is facilitated. Speed is not essential since the gravida will sleep until told to awaken. Posthypnotic suggestions are then given that she will be sound in mind and body and will have no after effect such as headache or pain. All patients wake up promptly when told to do so.

Advantages and Indications of the Use of Hypnosis in Labor

1. The procedure is relatively simple and no great amount of skill is necessary. Any physician can be taught the method.
2. No apparatus or expense is involved. It is the ideal method for home or hospital delivery.
3. There is absolutely no respiratory or circulatory depression in mother or fetus with resulting anoxia, asphyxia and cerebral damage.
4. Hypnosis raises the resistance to obstetric shock, circulatory and respiratory failure. Morphine, the barbiturates and paraldehyde act in the opposite way.
5. Resistance to fatigue and muscular effort during hypnosis is raised by more than 16 per cent, as shown by Williams.^{24, 25} Hence, there is little or no maternal exhaustion, which, undoubtedly is a contributing factor in the production of sepsis and shock.
6. The method is indicated when dealing with patients with a toxemia of pregnancy or cardiac decompensation or when a premature baby is concerned.

7. Complete hypotaxia or disassociation instead of hyperexcitability results from hypnosis. Patients are calm, quiet and relaxed. They usually make no noise even during the height of labor and delivery.

8. There is no depressant action on uterine contraction and retractions, as seen with most general anesthetics.

9. No untoward reactions such as delirium or jaetitation.

10. Analgesia and anesthesia are easily controlled. The patient can be told to awaken at any time. Most anesthetic agents such as intravenous evipal and barbiturates are beyond control once they are introduced into the body.

11. Postoperative recovery is smooth, and there is no danger of pneumonia, massive collapse of the lung, vomiting or coughing.

12. Blood loss is decreased during the hypnotic state probably due to a vasospastic condition of the capillaries or an effect on the blood coagulation time.

13. No injections are needed as with continuous caudal, spinal or local anesthesia. The latter are not without danger and require special skill.

14. The subjective pain element is not lost. Some contend that the pain of childbirth is a necessary psychological experience. The gravida can be awakened at any time and the progress of labor followed.

15. The method is a time saving procedure. The attention of the physician is not required if trained persons are available. Rapport can be transferred to an interne or nurse.

16. The amnesia, analgesia or anesthesia can be produced over the telephone, in suitably conditioned patients.

17. There is no increase in the incidence of operative delivery.

18. Complete relaxation or contraction of the abdominal wall and perineum can be produced simply by the command of the operator.

19. There is not the remotest possibility of danger to mother or baby.

The following case report is typical of our methods and results. Mrs. K. C., aged 20, last period May 2, 1942, at term February 9, 1943. Para 0, gravida i. She was first seen when 6½ months pregnant and was found to be normal, generally and obstetrically. The patient being quite intelligent was approached regarding the use of hypnosis. She was first hypnotized on November 2, 1942. Posthypnotic suggestions were given that the labor would be entirely painless, she would have no dread or anticipation for her confinement and would have a complete loss of memory for the entire experience. She was hypnotized bimonthly, 6 times before the onset of labor. Her prenatal period was uneventful, except for a rapid gain in weight, due to an uncontrollable appetite. Posthypnotic suggestions were utilized successfully to produce a loss of appetite, which resulted in a more normal weight gain. She wished to stop smoking; a few posthypnotic suggestions to the effect that she would vomit every time she tried to smoke, quickly produced the desired results.

Labor began at 4:30 A.M. on February 8, 1943. She entered the Chicago Lying-in Hospital 9:30 A.M. At this time she had 2 cm. dilatation,

the pains were ten minutes apart, of moderate intensity and regular. She was placed in a deep hypnotic state at 10:00 A.M. en rapport with Dr. Kroger. Labor progressed normally, during which time she asked to be fed and she urinated several times. She was deaf to the voice of her husband as well as the personnel on duty. She showed no sign of distress at any time. Rectal examinations produced no discomfort. The patient was completely disassociated as to time and place and talked only to Dr. Kroger. She complained of a slight backache. At 4:30 P.M. she vomited and awakened. At this time the cervix was dilated 9 centimeters. The pains were stronger and 1 minute apart. She was re-hypnotized at 4:35 P.M. She was then taken to the delivery room. The bag of water was artificially ruptured and she was asked to bear down.

A deep episiotomy and rather difficult low forceps were performed. The patient showed no sign of pain or distress, was completely relaxed and talked freely with the hypnotist (Dr. Kroger). An extensive perineorrhaphy was performed with the patient completely oblivious to what was happening. A silk-worm-gut repair was used and the patient was then awakened. She was visibly surprised at her surroundings, exclaiming, "Where am I, how did I get in here, don't tell me I have had a baby." She looked at the clock and asked, "Where have I been since ten o'clock this morning?" The entire labor and delivery was witnessed by various members of the staff. When interrogated by members of the staff as to her subjective experience she stated that her mind was a complete blank, and if they were to ask her to write her experience down she would have to hand them a blank piece of paper.

Her puerperium was uneventful, she had no knowledge that the stitches were present until the sixth day. On the following day amnesia and anesthesia were produced over the telephone by Dr. Kroger. Dr. DeLee removed the stitches and awakened her. She was completely amnesic and anesthetic for this experience. This was witnessed by interns, nurses, and members of the staff.

She regards her experience as most pleasurable and stated, "I can't see why more women don't have babies this way."

Discussion,

In a critical review of the world literature comprising hundreds of articles and books, not one authenticated fatality following the use of hypnosis has been reported.

Hypnosis has been relegated to an obscure position as an unexplained medical phenomenon because of popular disrepute by the laity.

Since medical men practice medicine according to the dictates of public policy, they hesitate to use this very valuable addition to our therapeutic armamentarium, not only because they are not conversant with its methodology, but because of the evil association of its origin.

How many more mothers and babies must die from anesthesia before the medical profession and laity will discard the prejudice and outmoded superstitions surrounding hypnosis?

From a practical standpoint, hypnosis fulfills all the desiderata of the ideal analgesic and anesthetic agent, namely, it alleviates suffering, does not interfere with the normal mechanism of labor and is safe for mother and baby.

The mechanism by which hypnosis and posthypnotic suggestion operates in relieving the pains of childbirth is fairly explainable, but requires a more fundamental type of investigation.

It may be considered that hypnosis is "synaptic ablation" and thus effectively blocks the somatic and autonomic pathways which transmit the afferent pain impulses to the higher sensorium. Another possibility is that through hypnosis, an effective control of the higher centers is exercised,²⁷ especially the fatigue, pain and memory centers in the hypothalamus. In some individuals, the pain threshold may be raised by hypnosis.

All physicians are aware of the powers of suggestions, and in the state of hypnosis, conscious resistance is reduced to a minimum. The patient is put in a state of heightened suggestibility and accepts suggestions without criticism.

Summary

Amnesia, analgesia and anesthesia were successfully induced in eleven patients. There was only one failure in our small series of cases. Ten of these were primiparas and one was a multipara. The hypnoidal state is a safe amnesic, analgesic and anesthetic agent. There are no untoward effects on the mother or baby and its many advantages are enumerated. Time worn superstitions, which prevent its use today by the medical profession should be discarded.

The value of the hypnoidal state in obstetrics should be assessed by others. Only then, can an objective evaluation be placed on its merits.

We desire to thank Drs. Wm. Dieckmann and J. P. Greenhill for their interest in this work.

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At the Zurich Clinic, the author found that from 1922 through 1941, there were 494 cases of thrombosis and embolism in the obstetric and 394 instances on the gynecologic services. The death rate in the obstetric series was only 1.4 per cent as contrasted with 12 per cent for the gynecologic series. The frequency of thrombosis and embolism following the various types of delivery was as follows: spontaneous delivery 1 per cent, all types of vaginal operative deliveries 2.6 per cent, forceps 4.2 per cent, manual removal of the placenta 5.2 per cent and cesarean section 7.2 per cent. The frequency of thrombosis and embolism among the gynecologic patients was as follows: vaginal operation 0.55 per cent, abdominal operations 3.5 per cent.

Among 35,204 labor cases the frequency of fatal embolism was 0.2 per cent and distributed as follows: one death for every 3,000 spontaneous deliveries, 1 death in 1,700 vaginal operative deliveries and 1 death after 300 cesarean sections.

The factors which are particularly favorable for thrombosis and embolism are age past 40, preoperative increase in sedimentation rate, malignancy, fibromyomas, cardiac circulatory diseases and varicosities and obesity.

Prophylactic measures are as follows: (1) Careful placing of indications for operation; (2) Early bed exercises following operation including massage, early rising, elevation of the foot of the bed; and (3) Abundant fluids postoperatively, alkali diet (chiefly fruits and vegetables) and where necessary stimulation of the circulation.

J. P. GREENHILL.

THE BASAL METABOLIC RATE, BASAL BODY TEMPERATURES, AND THE OVARIAN CYCLE*

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THOSE who have conducted any considerable number of basal metabolic determinations have inevitably experienced difficulty in basing the clinical dose of thyroid extract upon the basal metabolic reading. When the tolerance to thyroid extract is not in accord with what might be anticipated from the basal metabolic reading, the question arises as to a possible error in the conduct of the test, whether there might be some other condition than thyroid deficiency which has caused the low basal metabolic rate and in which thyroid extract is contraindicated, or whether there may have developed a peculiar lack of tolerance to thyroid extract in one who over a long period of time has become adjusted to a thyroid deficit. Such discrepancies are indeed so common that many physicians have lost confidence in the results obtained by the use of a metabolator and decide on the desirability of thyroid medication or surgery more upon clinical considerations. In the writer's cases, the rather arbitrary practice has been followed of estimating the thyroid dosage as one grain for about each 6 per cent reduction in the basal metabolic rate below a minus 10 per cent, and although this has worked satisfactorily as a rough measure of thyroid tolerance, there have been a number of cases with readings as low as minus 33 per cent that have failed to clinically tolerate as small a dose as 0.5 grain, while in others with a rate as high as minus 18 per cent have tolerated as much as 3 to 4 grains, and improved clinically in consequence. In all cases in which thyroid extract has been given, the weight and basal pulse rate has been recorded every two or three days and used as a guide for thyroid extract administration. The thyroid dosage was reduced if there was a marked increase in the pulse rate or a reduction in the weight or if other symptoms indicative of excessive thyroid dosage developed. In a few of the cases, the weight was reduced by dietary measures after the thyroid tolerance had been established, but not before.

Barnes¹ has suggested the employment of a record of basal body temperatures as a means of overcoming some of the failures inherent to the problem of establishing the correct therapeutic dose of thyroid extract. He states, "In over 1,000 cases in which the basal metabolic rate has been found subnormal, the body temperature has never been found up to normal unless an infection was present;" and he expressed the opinion that "subnormal body temperature is a better index for thyroid therapy than the basal metabolic rate."

*Presented at the Staff Meeting of the Springfield Hospital, May 12 1943.

This rather novel suggestion prompted the examination of some of my case records to see if this relationship pertained to them, and to determine whether the basal body temperatures* could be employed in routine clinical cases for regulating thyroid therapy. For this purpose 35 consecutive cases were studied. The data here presented are the result of that analysis. The basal metabolic rates of the 35 cases ranged from minus 34 per cent to plus 10 per cent, and all of them had had daily basal temperature recordings for periods ranging from 2 to 12 months. Some had received no thyroid extract, others thyroid extract during the entire period and still others for only part of the time. All were extremely healthy individuals although the appearance of two or three of them was mildly suggestive of hypothyroidism. None were outspoken hypothyroids. None of them presented any nutritive disorder or infection that might reasonably be expected to affect the temperatures or the basal metabolic rates.

Five out of the 35 cases received no thyroid extract. Their basal metabolic rates ranged from minus 22 per cent to plus 10 per cent. One of this group (Case No. 244, B.M.R., minus 16 per cent) presented an abnormally high temperature level because of pregnancy. The temperature levels of the rest were normal. (Table I.)

TABLE I. BASAL BODY TEMPERATURE RECORDS OF CASES RECEIVING NO THYROID EXTRACT

CASE NO.	B.M.R.	GRAINS THYROID	RANGE TEMP. SHIFT IN DAYS	MEAN OVULATION DAY	DAYS VARIATION IN OVULATION	GROSS CYCLIC TEMP. RANGE	MAXIMUM DEGREES TEMP. VARIATION	DEGREES OVULATION DEPRESSION
51	+4.5	0	5-21	16	16	97-99	2.0	0.2
167	-22	0	none	none	--	97.8-98.2	0.4	none
188	+10	0	11-14	13	3	97.5-98.8	1.3	0.3
237	-11.5	0	9-12	10	3	97.6-99	1.3	0.4
244	-16	0	none	none	none	98.6-99	0.4	none

In Table II is recorded the basal temperatures of 17 women whose basal metabolic rates ranged between minus 15 per cent and minus 4 per cent and who had received thyroid extract for a part or all of the period during which basal body temperatures were being recorded. One individual out of this group (No. 185, B.M.R., minus 12 per cent) presented low temperatures at ovulation time in 2 out of 8 cycles. The temperature levels of the other members of the group all fell within normal limits, in spite of the different basal metabolic rates and different sized thyroid dosage. Thyroid tolerance with various members of this group was attained with doses of thyroid extract ranging from 0.5 to 2 grains daily. Three cases (Nos. 220, 247, 257) ran temperatures slightly higher than the normal level during the proliferative phase of

*The cases were drawn from the female sterility studies in which daily basal body temperatures have been recorded for purposes of ovulation timing and the recognition of ovular diseases. Such studies are essentially routine in sterility work-ups and thus furnish an abundant record of basal body temperatures.

their cycles. All three gave evidence of abnormal ovulation, and the temperature levels were the same whether receiving thyroid extract or not. None of the cases have given any evidence of the ability of thyroid extract to elevate the temperature of cases with lowered basal metabolic rates.

With the thirteen cases whose basal metabolic rates ranged between minus 15 per cent and minus 34 per cent only one (No. 221, B.M.R. minus 19 per cent) presented abnormal temperature levels. This case, although having a basal metabolic rate of minus 19 per cent, tolerated

TABLE II. BASAL BODY TEMPERATURE RECORDS OF CASES WITH B.M.R. RANGING BETWEEN MINUS 15% AND MINUS 4%, AND GIVEN THYROID EXTRACT IN DIFFERENT SIZED DOSES

CASE NO.	B.M.R.	GRS. THYROID	RANGE OF TEMP. SHIFT IN DAYS	MEAN DAY OF OVULATION	DAYS VARIATION IN OVULATION	GROSS CYCLIC TEMP. RANGE	MAXIMUM DEGREES TEMP. VARIATION	DEGREES OVULATION DEPRESSION
177	0	½	15-21	17	6	97.4-99	1.5	0.4
184	-8.5	i	5-19	14	14	97.2-98.8	1.6	0.2
185	-12	½	10-19	12	9	96.6-98.6	2.0	0.3
187	-14	ii	12	12	—	97.5-98.6	1.0	0.3
204	-15	ii	7-15	12	8	97.0-99	2.0	0.4
217	-10	i	12-29	18	17	97.4-98.6	1.2	0.4
220	-7.5	i	9-18	13	9	98.2-98.9	0.7	0.3
229	-15	i	12-14	13	2	97.4-99	1.5	0.5
232	-11	½	12-17	14.5	5	97.5-98.9	1.4	0.5
233	-11	i½	9-10	9.5	1	97.8-99	1.1	0.2
242	-13.5	i	4-16	12	12	97.8-99.4	1.6	0.4
243	-15	ii	13-16	15	3	97.5-99	1.5	0.4
247	-15	i	10-22	16	12	98.0-99.2	1.2	none
251	-8.5	i	11-14	13	3	97.6-99	1.4	0.2
255	-13	ii	6-14	10	8	97.3-99	1.7	0.6
257	-15	i	none	none	none	98.0-98.6	0.6	none
258	-4	½	8-10	9	2	97.6-99	1.3	0.4

TABLE III. BASAL BODY TEMPERATURE RECORDS OF CASES WITH BASAL METABOLIC RATE RANGING BETWEEN MINUS 34% AND MINUS 16%, AND GIVEN THYROID EXTRACT IN DIFFERENT SIZED DOSES

CASE NO.	B.M.R.	GRS. THYROID	RANGE OF TEMP. SHIFT IN DAYS	MEAN DAY OF OVULATION	DAYS VARIATION IN OVULATION	GROSS CYCLIC TEMP. RANGE	MAXIMUM DEGREES TEMP. VARIATION	DEGREES OVULATION DEPRESSION
151	-22	ii	12-15	13	3	97.8-99	1.2	0.3
196	-30	ii	9-15	12	6	97.6-98.8	1.2	0.3
210	-26	ii	8-20	16	12	97.5-98.9	1.4	0.3
215	-16	i	11-33	13	22	97.4-98.8	1.4	0.3
219	-26	ii½	13-14	13.5	1	97.8-98.8	1.0	0.2
221	-19	½	9-15	12	6*	98.0-99.2	1.2	0.6
241	-20	ii	none	none	none*	97.6-98.6	1.0	none
245	-29	v	11-15	12	4	97.3-98.5	1.2	0.3
248	-34	v	11-18	14	7	97.3-98.8	1.5	0.7
249	-19	v	11-19	15	8	97.6-99	1.4	none
250	-18.5	iii	11-15	13	4	97.7-98.3	1.6	0.3
254	-24	iii	12-13	13		97.6-98.6	1.0	
259	-24	iv	11-16	13	5	97.2-98.2	1.0	0.4

*Usually very narrow range.

only 0.5 grain of thyroid extract daily. For 9 consecutive cycles during which 0.5 grain thyroid extract was administered part of the time, the temperature level was uniformly too high, and then the temperature level became normal. None of the cases with basal metabolic rates of minus 15 per cent or less ran any abnormally low temperatures during periods of from 2 to 12 months of daily temperature recordings.

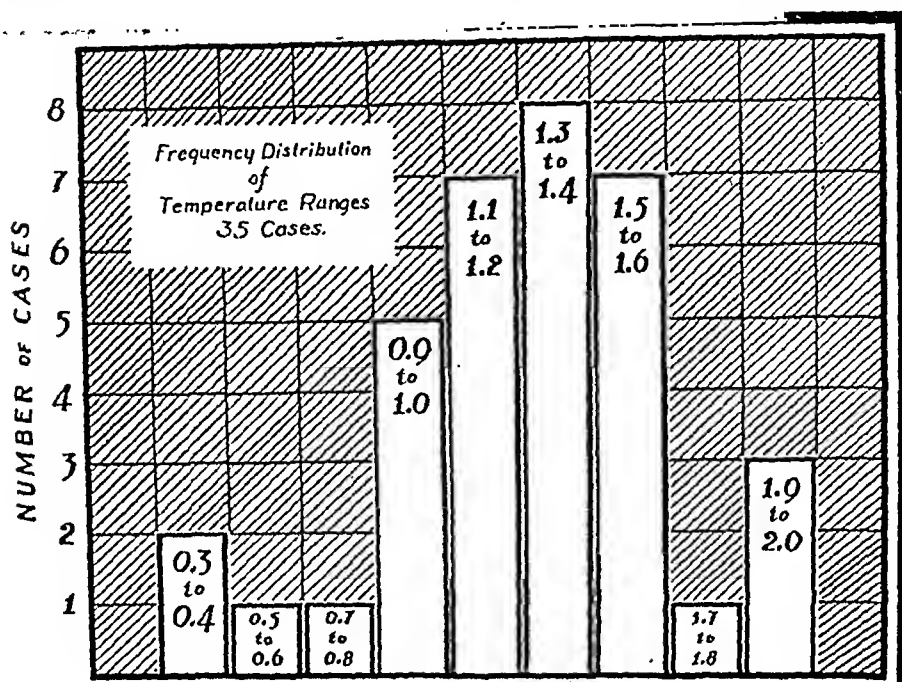


Fig. 1.—Frequency distribution of maximal cyclic temperature variations in 35 women.

In appraising the possible effect of the basal metabolic rate upon the basal body temperature of women, one must necessarily take into consideration the ordinary cyclic temperature variations of ovulating women. During the first half of the cycle an average temperature level of about 98 degrees is usually maintained, often followed by an abrupt but brief drop of 0.3 to 0.4 degrees and then a shift to a higher temperature level which continues at about 98.5 degrees until one to three days before the onset of the next menses. The time of the shift from the low to the high temperature plateau marks the time of ovulation. This general temperature pattern is quite constant to normal ovulating women, but varies greatly with pathologic ovulation. Normal ovulating women commonly present each cycle a temperature variation of 0.9 to 1.6°. The low point falls on the day of ovulation, the high point a few days later and the variation ranges between about 97.2 and 99 degrees Fahrenheit. Therefore, normal temperature variations of ovulating women cannot be considered as pathologic unless they are not the result of the normal ovarian cycle. (Figs. 1 and 2.) The temperatures of all the 35 cases cited in this paper kept within

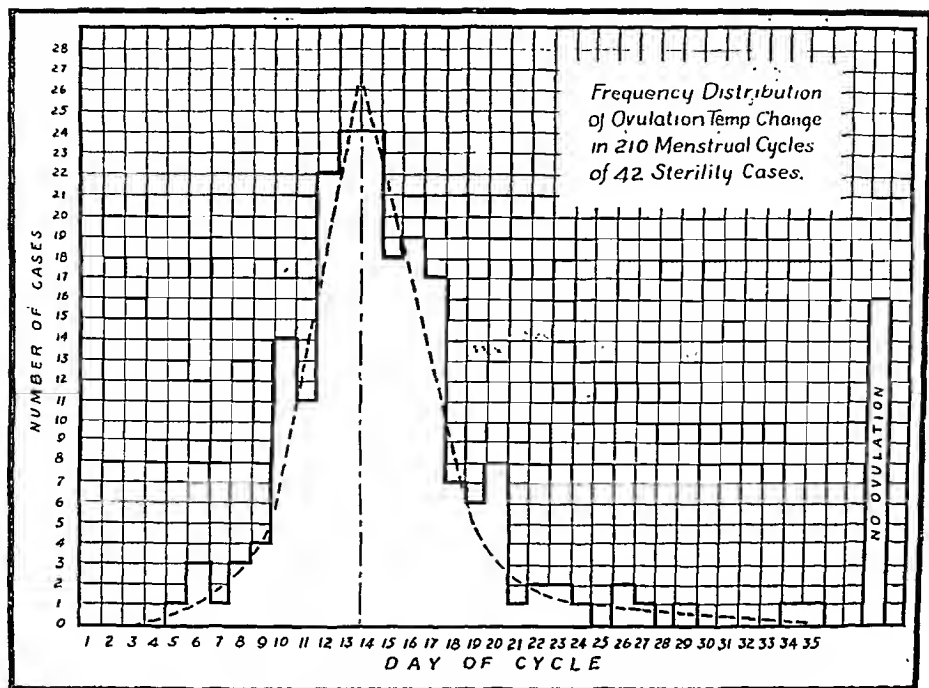


Fig. 2.—Frequency distribution of ovulation temperature change with forty-two women, 210 cycles.

this range of normal variability excepting for a few sporadic temperatures due either to ovulation or illness.*

If the basal metabolic rates within the ranges here presented were capable of affecting the temperature level, one should expect to find that the group of cases with the lower basal metabolic rates would present over a period of several months with daily temperature recordings, a somewhat lower average minimal and maximal temperatures

TABLE IV. RELATION OF THE BASAL METABOLIC RATE TO THE AVERAGE MINIMAL AND MAXIMAL TEMPERATURES RECORDED WITH 42 CASES WITH DAILY TEMPERATURE READINGS COVERING 210 MENSTRUAL CYCLES

	AVERAGE MINIMAL TEMP.	AVERAGE MAXIMAL TEMP.	MAXIMUM DEGREES TEMP. VARIATION
B.M.R. Minus 22% to plus 10%. No thyroid extract. (5 cases)	97.7	98.8	1.1
B.M.R. Minus 15% to minus 4%. Thyroid extract to clinical tolerance in part of cycles. (17 cases)	97.5	98.9	1.4
B.M.R. Minus 16% to minus 34%. Thyroid extract to clinical tolerance in part of the cycles. (13 cases)	97.6	98.7	1.1

*Since the preparation of this paper, a record of the basal body temperatures and the basal metabolic rate has been obtained with an additional 70 women. Two of these had uniformly lower basal body temperatures than previously encountered, one with temperatures ranging between 96.6 and 97.8, the other between 97.2 and 98 degrees throughout two to three cycles. The former had a B.M.R. of plus 5 per cent, and the latter a B.M.R. of plus 12 per cent. This is rather the opposite effect to what might be anticipated, that the cases with the higher B.M.R. of the series should present the lowest basal body temperatures.

than the group of the series with the higher basal metabolic rates. Such, however, was not the case. (Table IV.) Again comparing the extremes of basal metabolic rates of the series, it is found that the case with the highest rate (No. 188, B.M.R. plus 10 per cent) had a temperature range of 97.5 to 98.8 degrees, in contrast to a temperature range of 97.8 to 98.2 degrees with the case with the lowest B.M.R. that received no thyroid extract (Case No. 167, B.M.R. minus 22 per cent), suggesting that a difference of as little as 30 to 40 per cent in the basal metabolic rate is hardly sufficient to influence the basal body temperature level.

Summary

The records of 35 routine clinical cases with basal metabolic rates ranging between plus 10 per cent and minus 34 per cent were examined to determine (1) what if any relationship existed between the basal metabolic rates and the basal body temperatures, and (2) the feasibility of using basal body temperatures as an index to thyroid therapy. These studies have not confirmed Barnes' observation of the relationship between the basal body temperature and basal metabolic rate, nor given any evidence that the basal body temperatures of this series of cases has been influenced by the administration of thyroid extract in doses as high as could be clinically tolerated.

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Barns, H. H. Fouracre: Maternal Birth Palsy Due to Trauma, J. Obst. & Gynaec. Brit. Emp. 50: 13, 1943.

The author reports three cases of maternal birth palsy. A general review of the etiology of this condition is given. The lumbosacral cord is compressed, as it lies on the ala of the sacrum, by the fetal head. Instrumentation and repeated attempts at forceps delivery in difficult labors may aggravate this condition. The author describes the clinical syndrome. The chief clinical signs are severe cramps and pain or paresis in the legs during labor. The author goes as far as advising cesarean section in such patients where the danger of instrumentation might aggravate the above symptoms. This is especially true if the child is normal and alive.

WILLIAM BERMAN.

THE TRANSFER OF SODIUM ACROSS THE HUMAN PLACENTA

Preliminary Report

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THIS investigation was undertaken with the view of establishing in man the characteristics of placental transfer of sodium at various stages of gestation both in normal and pathological conditions. Eleven observations in 10 cases are now at hand. This is an inadequate series for the original purposes of the study. The observations, together with tentative comments, are recorded here, however, because they are unique and were obtained only after considerable effort and expense, and because it is improbable that the studies can be resumed for some time to come.

The observations were made in 10 pregnant women in whom pregnancy was terminated by abdominal hysterotomy. The indications for operation are listed in the table. Radiosodium present as the chloride in isotonic solution with an activity of 0.3 to 0.5 millicurie, was injected intravenously into the mother. This amount of radioactivity is known to be innocuous to mother and fetus.^{1, 2} At a known interval of time after injection, usually 30 minutes, fetus and placenta were delivered and a sample of maternal venous blood was taken. Radioactivity in the maternal plasma and the ashed remains of the non-viable fetus was measured with a pressure ionization chamber-string electrometer.³ When a viable fetus was obtained, a sample of fetal blood was taken by venipuncture after time was allowed for equilibration of the radiosodium within the extracellular fluids and the radioactivity of the blood sample was then measured. The total radiosodium transferred to the fetus in such an instance was calculated on the assumption that 30 per cent of the body weight was available for dilution of the radiosodium.⁴ The rate of transfer of sodium was derived from these data as previously noted.⁵ The duration of gestation was calculated from the menstrual history.

The observations are presented in the table and permit two tentative conclusions. In both those cases where placental transfer is judged to approach closely the normal (cases 1, 3, 5, 7, 9, 10) and in those remaining where abnormal alterations may be more readily suspected,

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there is clearly an increase in rate of transfer per unit weight placenta with increase in gestation age. The overall increase, noted from 10 to 38 weeks, is 7 times. This finding corresponds qualitatively with that observed in all placentas previously studied.^{3, 6-10} It is also apparent from the table and from previously published data that the rate of transfer of sodium per gram placenta per hour in man appears to be closely like that reported for other hemochorial placentas at corresponding periods of gestation.^{3, 5-7}

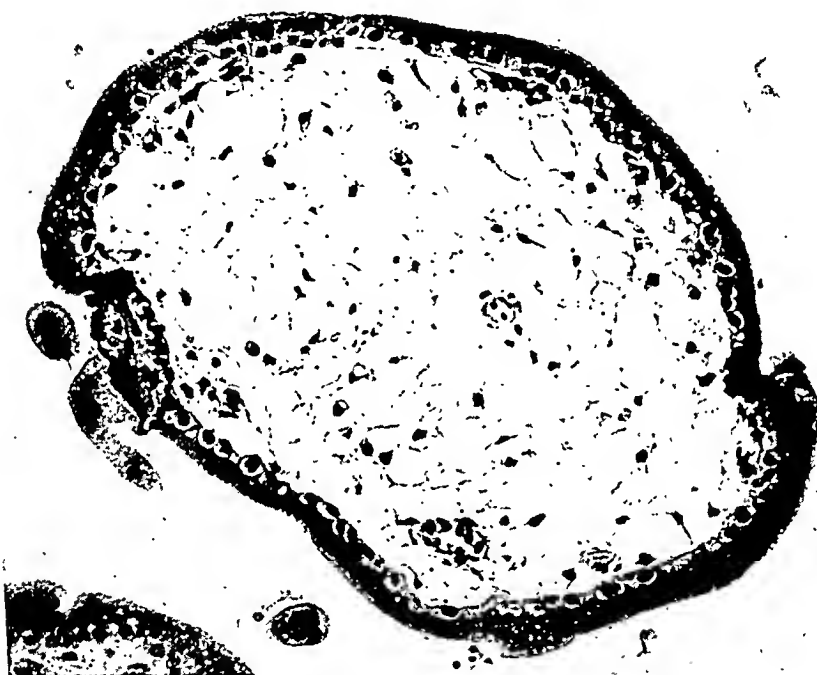


Fig. 1.—Human placenta from 12 weeks' pregnancy. $\times 000$.

TABLE I

CASE NO.	HISTORY NO.	INDICATION FOR OPERATION	GESTA-TION AGE	WEIGHT FETUS (GM.)	WEIGHT PLA-CENTA (GM.)	TOTAL Na TRANS. TO FE-TUS/HR. (MG.)	TRANS-FER Na/GM. PLACEN-TA/HR. (MG.)
1	231656	Schizophrenia	10 wks.	36.0	63.0	48.5	0.76
2	240415	Chronic nephritis	12 wks.	14.3	33.6	46.0	1.37
3	257328	Epilepsy	12 wks.	19.0	33.5	19.1	0.57
4	165446	Chronic hypertension	16 wks.	129.4	100.0	170.5	1.70
5	247063	Schizophrenia	16 wks.	402.3	126.0	295.0	2.34
6	259938	Chronic hypertension	20 wks.	361.1	140.4	400.0	2.85
7	249863	Feeble-minded	20 wks.	544.5	156.1	726.0	4.66
8	250383	Chronic hypertension	24 wks.	613.5	168.0	802.0	4.76
9	260095	Previous section	37 wks.	2,180.0	213.5	1,036.0	4.86
				2,030.0	205.0	370.0	3.41
10	103003	Previous section	38 wks.	2,700.0	370.0	1,966.0	5.32

This increase in rate of transfer of sodium per unit weight placenta with increase in gestation age can be related to morphological changes which occur as the placenta ages. The photomicrographs in Figs. 1, 2, 3, and 4 are typical of placentas of 12, 19, 28, and 37 weeks. They are all taken at the same magnification and show clearly some of the important alterations in this organ as gestation progresses. At 12 weeks, the villi are large, relatively few in number and covered with a double layer of cells, the outer, syncytial and the inner, cellular known as Langhans' layer. At 19 weeks, there is an increase in the



Fig. 2.—Human placenta from 19 weeks' pregnancy. $\times 000$.

number of villi, a decrease in their size and the Langhans' layer has almost completely disappeared. The increase in number and decrease in cross-sectional area of villi, together with thinning of their walls, continues through the twenty-eighth week to term. Higher magnification reveals in addition, as pregnancy proceeds, an increase in number of fetal capillaries within the stroma of the villus together with a decrease in the thickness of the capillary walls. All of these morphological changes provide an interpretation of the increase in transfer rate per unit weight placenta which has been observed as pregnancy progresses.

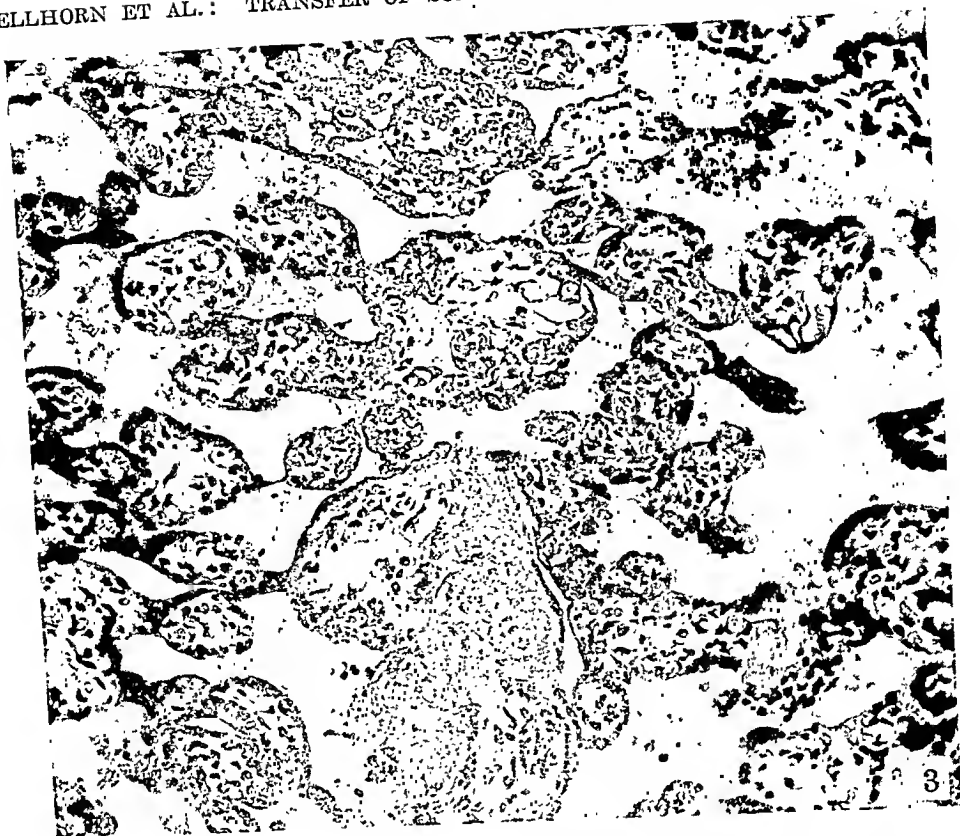


Fig. 3.—Human placenta from 28 weeks' pregnancy. $\times 000$.



Fig. 4.—Human placenta from 40 weeks' pregnancy. $\times 000$.

Conclusions

Although the data are insufficient for precise quantitative conclusions, they indicate that in man the rate of transfer of sodium per unit weight placenta increases markedly as gestation proceeds. This change can be correlated with morphological changes which occur in the human placenta. Sodium appears to be transferred across a unit weight of the human placenta at about the same rate found in other hemochorial placentas at corresponding periods of gestation.

We are grateful to Dr. N. J. Eastman for his interest and generous cooperation. We also wish to express our warm appreciation to Dr. B. R. Curtis, Department of Physics, Harvard University, for preparing the radiosodium in the Harvard cyclotron.

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RECTAL STRICTURE COMPLICATING LABOR

An Analysis of Forty-Eight Cases

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STRICTURE of the rectum as a complication of labor has received increasing attention in recent years as its potential gravity has become recognized. The literature on the subject to date consists of reports of thirty labors, and this paucity of material makes evaluation of the problems involved difficult. It was therefore decided to review the experience of the department of obstetrics of the Johns Hopkins Hospital, which comprises forty-eight labors complicated by rectal stricture.

Review of Literature

The earliest reference to stricture of the rectum complicating labor is apparently that by Dorsett¹ in 1920. The case is an excellent example of the syndrome associated with rupture of the rectum. The patient was a 37-year-old para iii, gravida iii, who had been delivered at home

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by forceps. Shortly thereafter she complained of severe pain in the left side and went into shock. About twelve hours post partum, signs of generalized peritonitis appeared and the patient was transferred to the hospital. She was found markedly distended with all signs of peritonitis and died shortly after admission, forty-two hours post partum. Autopsy revealed stricture of the rectum with transverse rupture into the peritoneal cavity at the rectosigmoid junction.

Kassebohm and Schreiber² reported two further deaths in 1936. One occurred in a para ii, gravida ii, who had a stricture and rectovaginal fistula. The patient delivered spontaneously after an uneventful labor, but seven hours post partum was found in profound shock with abdominal distention and rigidity. She died nine hours thereafter, and autopsy revealed rupture of the rectum. Their other case was a primipara delivered by midforceps who died early post partum. No autopsy is described.

The fourth fatal case is that of Gaines and MacDowell,³ reported in 1936. The patient was a 19-year-old primipara who fell into labor spontaneously at term. She was found to have a rectal stricture admitting a fingertip and involving the rectovaginal septum. Maternal condition was poor during labor and when the fetal vertex crowned, forceps were attempted unsuccessfully. Delivery was accomplished by version and extraction. The mother went rapidly into shock, with signs of peritonitis, and died five and one-half hours post partum. Autopsy revealed rupture of the rectum into the peritoneal cavity. On the basis of this case, the authors recommend cesarean section for delivery of these patients.

Kassebohm and Schreiber⁴ in 1937 reported a series of eighteen labors including the two deaths reported in their paper of 1936. The eighteen cases resulted in fifteen spontaneous deliveries and three forceps operations. Drawing attention to the excessive maternal mortality, they recommend therapeutic abortion where feasible in all patients with rectal stricture, delivery with wide or bilateral episiotomy and routine sterilization.

Anderson⁵ in 1938 reported a fifth death. The patient was 22 years old and had had a previous difficult forceps delivery. She was found to have a rectal stricture with thickening of the rectovaginal septum, and a rectovaginal fistula. After twelve hours of labor, with the cervix almost fully dilated and membranes ruptured for nine hours, the fetus was delivered by version and extraction. Uterine exploration revealed rupture of the uterus in the lower uterine segment. The rupture was repaired at laparotomy, but the patient died in eight hours. In the same year, Michelson⁶ reported a normal uncomplicated delivery in a patient with rectal stricture.

Vignes,⁷ in 1939, reported two further cases. One was delivered by cesarean section for malpresentation and was found to have rectal stricture post partum. The second had a sixty-two hour labor terminated by a difficult forceps delivery. This was followed by signs of peritonitis and death in thirteen hours. No autopsy was obtained, but exploration proved the birth canal to be intact. The same author refers elsewhere⁸ to a patient with colostomy for rectal stricture who suffered no complications in her three deliveries. This is the only case recorded in the literature of a patient who had more than one delivery in the presence of rectal stricture. In 1940, Vignes⁹ reported a

30-year-old primipara who was found to have a stricture and recto-vaginal fistula after eleven and one-half hours of poor labor and was treated by radical cesarean section, with recovery. Fagarasano,¹⁰ in the same year, reported a patient in whom he performed an abdomino-perineal bowel resection for rectal stricture with re-establishment of a perineal rectum. The patient delivered a 2,860 Gm. infant uneventfully seven months later.

The most recent report is that of Pollard and Hellendahl¹¹ in 1942. The patient, a secundipara, was delivered by breech extraction. Four hours post partum cramps and signs of peritonitis developed; death occurred twenty-one hours post partum. Autopsy revealed rupture of the rectum. These authors suggest bowel surgery early in pregnancy.

These thirty labors are presented in summary form in Table I.

Experience of the Johns Hopkins Hospital

Forty-eight deliveries in thirty-one patients suffering from rectal stricture, with one maternal death, have been found in the records of the Johns Hopkins hospital. More than one-third of these cases have been observed in the last five years. Labors not occurring under the supervision of the department of obstetrics have been excluded from this study.

At the time of delivery the parity of the patients was:

Para 0:11 cases

1:10

2:9

3:5

4:7

5:4

6:1

7:1

Twenty-three patients, or 73 per cent of the entire group, have had but one delivery under our observation after the diagnosis of rectal stricture. Three patients have had two deliveries, one has had three, and four had four deliveries. The series of multiple deliveries is therefore small, and no conclusions as to the effect of multiparity on rectal stricture can be reached. No patient suffered an exacerbation of the rectal stricture during pregnancy.

Sixteen patients, or 52 per cent of the thirty-one, had proved syphilis at some time, as compared with a rate of 22 per cent for the past five years among Negro dispensary patients. The latter group will be used as a control series throughout this study, since thirty of the thirty-one patients and forty-seven of the forty-eight deliveries occurred in Negro women. This high rate of syphilis is not remarkable in a series of patients, the majority of whom have suffered from lymphopathia venereum.

Thirty-one deliveries occurred in patients with normal pelves, thirteen in the presence of slight contraction, and three in patients whose diagonal conjugate was 10.5 cm. One pelvis was unmeasured.

Detailed information about the rectal strictures in this series is not to be found in the records, unfortunately, except in a few recent cases. Many are described only by the statement that the stricture would not "admit a fingertip." It can be stated, however, that twenty deliveries, or 43 per cent, occurred in the presence of a rectal stricture which would not pass a fingertip at some time prior to delivery, or one asso-

TABLE I. THIRTY LABORS IN THE PRESENCE OF RECTAL STRICTURE RECORDED IN THE LITERATURE

AUTHOR	AGE	PARITY	DURATION OF LABOR	TYPE OF DELIVERY	FETAL WEIGHT	COMPLICATIONS
1. Dorsett	37	3	?	Forceps	?	Peritonitis and death—rupture of rectum proved at autopsy
2. Kassebohm and Schreiber	32	2	3+ Hrs.	Spontaneous	5-11	Peritonitis and death—rupture of rectum proved at autopsy
3. <i>ibid.</i>	24	0	?	Midforceps	?	Death early post partum—no autopsy
4. Gaines and MacDowell	19	0	24	Version	3060	Peritonitis and death—rupture of rectum proved at autopsy
5. Kassebohm and Schreiber	31	3	?	Spontaneous	5-7	Febrile puerperium
6. <i>ibid.</i>	24	2	?	Spontaneous	6-6	Febrile puerperium
7. <i>ibid.</i>	26	0	?	Spontaneous	5-1	
8. <i>ibid.</i>	31	5	?	Spontaneous	7-12	Febrile puerporium
9. <i>ibid.</i>	26	1	?	Cesarean	6-12	Febrile puerperium
10. <i>ibid.</i>	29	0	?	Midforceps	7-6	
11. <i>ibid.</i>	20	0	?	Spontaneous	7-7	
12. <i>ibid.</i>	26	2	?	Spontaneous	5-7	
13. <i>ibid.</i>	22	1	?	Spontaneous	7-14	Febrile puerperium
14. <i>ibid.</i>	29	4	?	Spontaneous	6-5	Febrile puerperium
15. <i>ibid.</i>	22	3	?	Spontaneous	6-6	
16. <i>ibid.</i>	20	1	?	Spontaneous	5-7	
17. <i>ibid.</i>	31	1	?	Spontaneous	8-4	
18. <i>ibid.</i>	25	0	?	Spontaneous	2-13	Febrile puerperium
19. <i>ibid.</i>	23	5	?	Spontaneous	7-3	
20. <i>ibid.</i>	25	2	?	Version	7-4	
21. Anderson	22	1	12		?	Rupture of uterus, laparotomy and repair, death in shock
22. Mielleson et al.	34	0	?	?	?	Partial bowel obstruction in puerperium
23. Vignes	?	0	?	Cesarean	?	Early death post partum—uterus, cervix and vagina intact—no autopsy.
24. <i>ibid.</i>	?	?	62	Forceps	?	(This case, and No. 26 and No. 27 all in the same patient). Colostomy
25. Vignes	?	?	?	Spontaneous	?	
26. <i>ibid.</i>	?	?	?	Spontaneous	?	Multiple perineal fistulas, severe stricture and dystocia
27. <i>ibid.</i>	?	?	?	Spontaneous	3050	Delivery 7 months after bowel resection and perineal colostomy
28. Vignes	30	0	13	Cesarean	2860	Peritonitis and death—rupture of rectum proved at autopsy
29. Fagarasano	?	?	?	Spontaneous	?	
30. Pollard et al.	32	1	8½	Breech	?	

ciated with a rectovaginal fistula. In twenty-two cases, lesser degrees of stricture existed. In five, no description is available except that a stricture was present. Two patients suffered rectovaginal fistula, and one had severe lymphopathia venereum with multiple perineal fistulas. Another suffered elephantiasis of both legs. Two patients came to delivery with previous colostomies, and one of these had had a previous ablation of the rectum.

Other ante-partum complications observed in these forty-eight pregnancies were few in number, and so clearly incidental that they require no detailed description.

At the onset of labor, forty fetuses, or 83 per cent, were in normal vertex presentation and three in breech. One premature fetus lay in a transverse position. In four the presentation was not stated.

Method of delivery was as follows: spontaneously by vertex: thirty-four deliveries, or 71 per cent; forceps to the vertex including one mid-forceps: five deliveries, or 10 per cent; breech extraction: three deliveries, or 6 per cent; version and extraction: one delivery; spontaneous evolution of a compound presentation; one fetus. There were five cesarean sections, or 10 per cent. This is approximately twice the clinic average.

The duration of labor in the forty-three pelvic deliveries comprising this series is compared in Table II with Peckham's data¹² for 7,117 such deliveries in Negroes at the Johns Hopkins Hospital.

TABLE II

TIME (HOURS)	0-11	12-17	18-23	24-29	30—	TOTAL
Peckham's series—%	46.32	23.00	12.63	8.12	9.92	99.99
Expected cases in 43 cases according to Peckham's data	20.0	9.9	5.3	3.5	4.3	43.0
Observed	17	13	5	5	3	43.0

This comparison has been carried out with corrections for parity and the differences are not statistically significant. There is no evidence therefore that rectal stricture is associated with prolongation of total labor.

Duration of the second stage in this group is compared in Table III with a series of 795 deliveries, made up of all pelvic deliveries in Negroes in this hospital in 1942.

TABLE III

HOURS	0-½	½-2	2-3	3-4	4—	UN-KNOWN	TOTAL
Control—%	47.3	34.3	3.1	0.9	1.1	13.5	100.2
Expected cases in 43 at control rates	20.3	14.7	1.3	0.4	0.5	5.8	43
Observed	12	11	3	0	2	15	43.0

There is, therefore, no significant incidence of prolonged second stage. Three patients with little scarring of the pelvic soft tissues manifested uterine inertia throughout labor, and in each case the prolonged second stage was associated with failure of the vertex to rotate. Another, with a dense stricture, had uterine inertia in the second stage

of her third-term delivery and delivered uneventfully on three subsequent occasions. In the two other patients in whom the second stage lasted over 2 hours, there is no satisfactory explanation for the prolongation of the labor.

Intrapartum and post-partum complications were largely incidental. The instance of compound presentation eventuated in spontaneous evolution, Case 2 in Stephenson's¹³ report. The one maternal death resulted from spontaneous rupture of the uterus.

Febrile puerperia were observed in eighteen instances, or 37 per cent, as compared with 24 per cent in the control group. Two patients suffered severe puerperal pelvic infection. In one, this followed multiple unsterile vaginal examinations done elsewhere. In the other, no satisfactory explanation was found. However, since she developed a pelvic mass post partum, it is conceivable that she suffered an unrecognized rupture of the rectum outside the peritoneum into the soft tissues of the pelvis. There is no proof for this conjecture.

There was no impairment of bowel function in the puerperium as compared with the patients' function previously or with the control series.

Sterilization was performed in seven instances, four by tubal operation and three by hysterectomy; four accompanied cesarean section.

It should be mentioned that of the fourteen patients in whom a Frei or similar test was performed, thirteen were positive reactors.

The fetuses ranged in weight from 750 to over 4,000 grams, distributed similarly to those in the control group. Neonatal deaths occurred in two fetuses, 750 and 1,600 grams respectively in weight. There were five stillbirths, two in the same syphilitic mother. One stillbirth occurred in the instance of spontaneous evolution. Another was attributable to difficult breech delivery in a primigravida with contracted pelvis, Case 4. The fifth was associated with the maternal death due to ruptured uterus, Case 10.

More detailed information concerning these 48 labors is presented in Table IV.

Discussion

Rectal stricture may be the result of lymphopathia venereum, syphilis, tuberculosis, and other rarer causes. For all practical purposes, lymphopathia venereum has been accepted as the common cause of the dense scarring which reduces the lumen of the rectum, thickens its wall, and tends to immobilize the soft tissues of the pelvis. Further, in many instances, the infection spreads to involve the rectovaginal septum, scarring it and occasionally resulting in fistula formation.

Estimation of the importance of stricture as a cause of dystocia depends on careful examination and description not only of the caliber of the stricture but also of the status of the rectovaginal septum, of the location of the stricture, of the consistency of the scar tissue and of its extent in the connective tissue of the pelvis. A dense, pin-point stricture which is above the pouch of Douglas and unassociated with the pelvic scarring can hardly cause dystocia, and a soft, early stricture is also likely to be benign. A widely patent stricture densely fixed in the pelvis and involved in its retroperitoneal portion is a for-

TABLE IV. FORTY-EIGHT LABORS IN THE PRESENCE OF RECTAL STRICTURE OBSERVED AT THE JOHNS HOPKINS HOSPITAL

PATIENT YEAR	AGE	DURATION OF LABOR			TYPE OF DELIVERY	FETAL WEIGHT	PUERPERIUM	COMMENTS
		PARTY	SEC- OND STAGE	TOTAL				
1a. B. H. 1935	23	1-0-1-0-1	20	7-55	Vertex spontaneous	2,970	Afebrile	Severe rectal stricture.
1b. B. H. 1937	25	2-1-1-0-2	7	24-00	Vertex spontaneous	2,860	Afebrile	
1c. B. H. 1939	27	3-2-1-0-3	60	4-25	Vertex spontaneous	3,060	Afebrile	
1d. B. H. 1942	30	4-3-1-0-4	43	6-09	Vertex spontaneous	2,860	One-day fever	Post-partum tubal sterilization because of multiparity in the presence of slowly progressing stricture.
2. N. J. 1914	26	1-1-0-0-1	?	26-00	Spontaneous evolu- tion, compound presentation	2,500	Febrile	Stillborn. Note that the relatively large mass of a fetus undergoing spontaneous evolution passed through the birth canal evidently without rupturing the rectum.
3a. L. H. 1933	18	0	?	16-55	Vertex spontaneous	2,260	One-day fever	Severe stricture.
3b. L. H. 1935	20	1-0-1-0-1	10	4-20	Vertex spontaneous	1,425	Febrile	High fever on first post-partum day, per- sisting for two weeks. Mass in pelvis with birth canal apparently normal and intrauterine culture sterile. No satisfac- tory diagnosis. Eventual recovery.
3c. L. H. 1938	22	2-0-2-0-1	60	16-35	Vertex spontaneous	2,680	Endometritis	
3d. L. H. 1942	26	3-1-2-0-2	2	20-40	Vertex spontaneous	750	Afebrile	Fetus died on fourth day.
4a. M. W. 1920	25	4-0-4-0-0	55	9-00	Breech extraction	2,900	Afebrile	C.D. 10.5 em. Stillborn. Another example of a large fetal mass passing through the birth canal uneventfully. Severe stricture.
4b. M. W. 1923	28	5-1-4-0-0	170	13-10	Vertex spontaneous	2,380	Afebrile	

	25	1-0-0-1-0	172	38-16	Operative low forceps	3,370	Afebrile	Colostomy. Severe pre-eclampsia. Vertex failed to rotate, and, because of stretching of rectovaginal septum noted at delivery, delivered by forceps in transverse.
5. C.C. 1942								
6. O. H. 1940	27	1-1-0-0-0	85	28-28	Operative low forceps	2,310	Afebrile	Previous abdominoperineal operation for ablation of rectum and colostomy. Uterine inertia in labor treated by pituitrin stimulation and forceps delivery. Postpartum tubal sterilization.
7a. V. T. 1934	19	1-0-0-1-0	?	16-30	Breech extraction	2,470	One-day fever	Severe stricture.
7b. V. T. 1938	23	2-0-1-1-1	-	-	Low cervical cesarean	3,145	Endometritis	Development of multiple perineal and rectovaginal fistulas and dense fixation of rectum and perirectal tissues necessitated delivery by cesarean section. Tubal sterilization.
8. M. N. 1942	31	0	-	-	Low cervical cesarean	2,570	Afebrile	Severe rectal stricture. Precolostomy established at section.
9. S. O. 1938	36	1-1-0-0-1	-	-	Classical cesarean	2,180	Endometritis	Severe urinary tract infection, chronic bronchitis and partial intestinal obstruction late in pregnancy which failed to respond to therapy necessitated cesarean section.
10. H. F. 1914	32	4-4-0-0-4	?	19-00	Vertex spontaneous	3,630	Mortality	Colostomy established and tubal sterilization at same operation. Rectovaginal fistula. Severe rectal stricture. Found at home lying on floor following precipitate delivery accompanied by severe pain. Placenta readily expressed. Patient left in pain but in good condition. Found later having bled 700 c.c., in deep shock. Transferred to hospital but died before treatment, in 3 hours. Autopsy revealed lower uterine segment rupture. Fetus stillborn.
11a. E. S. 1912	28	3-2-1-0-0	50	4-55	Vertex spontaneous	?	Afebrile	Stillborn syphilitic premature, no data on stricture.

TABLE IV—CONT'D

PATIENT, YEAR	AGE	PARITY	DURATION OF LABOR		TYPE OF DELIVERY	FETAL WEIGHT	PUERPERIUM	COMMENTS
			SEC. OND STAGE	TOTAL				
11b. E. S. 1913	29	4-2-2-0-0	?	20-00	Vertex spontaneous	1,600	Afebrile	Fetus died on seventh day.
11e. E. S. 1915	31	5-2-3-0-0	?	1-30	Spontaneous	920	Afebrile	Stillborn.
12. F. V. 1916	32	1-0-0-1-0	9	30-19	Vertex spontaneous	2,320	Afebrile	Post-partum hemorrhage 1,100 c.e.; marked rectal stricture.
13a. I. K. 1923	28	4-2-0-2-0	290	10-00	Operative midforeeps	3,250	Endometritis	Uterine inertia in second stage; gonocoeal endometritis; dense rectal stricture.
13b. I. K. 1925	29	6-3-0-3-1	?	7-44	Vertex spontaneous	3,800	Afebrile	
13c. I. K. 1927	32	7-4-0-3-2	15	8-30	Vertex spontaneous	3,300	Afebrile	Unelassified toxemia.
13d. I. K. 1933	36	10-5-0-5-3	29	12-30	Vertex spontaneous	2,920	Afebrile	Hysterectomy for repeated toxemia.
14a. A. L. 1923	36	4-4-0-0-3	30	12-34	Vertex spontaneous	3,520	Afebrile	Slight rectal stricture; elephantiasis, both legs.
14b. A. L. 1925	38	5-5-0-0-4	?	16-45	Vertex spontaneous	2,100	Afebrile	
14c. A. L. 1926	39	6-5-1-0-5	45	5-00	Vertex spontaneous	3,630	Afebrile	
14d. A. L. 1929	42	7-6-1-0-6	5	?	Vertex spontaneous	3,025	Afebrile	Probably rapid labor.
15. Q. J. 1924	31	0	56	27-56	Vertex spontaneous	3,380	Endometritis	Dense stricture with repeated dilatations.
16. J. H. 1926	30	0	?	21-46	Breech extraction	2,425	Endometritis	No data on stricture.
17. L. M. 1928	19	2-2-0-0-2	?	17-04	Vertex spontaneous	2,500	One-day fever	Dense stricture; subsequent salpingectomy for P.I.D.
18. L. A. 1929	19	0	?	5-40	Vertex spontaneous	3,070	Afebrile	Dense stricture.

		27	1-1-0-0-0	-	-	Radical cesarean	3,665	Febrile	C.D. 10.5; craniotomy in previous labor; cervical atresia at term; dense rectal stricture.
19. F. B. 1929									
20. M. M. 1934	29	4-3-1-0-3	?	25-20	?	Version and extrac- tion	2,250	Afebrile	Placenta previa; induced labor with Voor- hees bag; version and extraction through incompletely dilated cervix; slight stric- ture.
21. M. H. 1934	22	3-2-0-1-2	20	12-50		Vertex spontaneous	3,365	Afebrile	Dense stricture with repeated dilatations.
22a. C. S. 1935	28	2-1-1-0-1	17	18-18		Vertex spontaneous	3,170	One-day fever	Dense stricture.
22b. C. S. 1942	35	5-2-1-2-2	31	8-25		Vertex spontaneous	2,800	Afebrile	
23. Q. B. 1938	24	0	40	8-42		Vertex spontaneous	2,750	One-day fever	No data on stricture.
24. M. M. 1939	23	3-2-0-1-2	?	5-30		Vertex spontaneous	3,030	One-day fever	Slight stricture; mastitis.
25. N. G. 1941	31	2-1-0-1-0	5	13-45		Vertex spontaneous	2,160	Afebrile	Dense stricture; rectovaginal fistula; pre- eclampsia.
26. E. H. 1942	26	1-0-0-1-0	?	14-34		Operative low forceps	2,570	Afebrile	Slight stricture; intrapartum pre-eclampsia.
27. M. W. 1942	39	3-2-0-1-2	-	-		Radical cesarean	2,980	Febrile	Very dense stricture involving rectovaginal septum.
28. E. F. 1942	18	0	55	15-00		Vertex spontaneous	2,820	Afebrile	Early slight stricture.
29. T. B. 1942	19	0	320	12-35		Vertex spontaneous	2,870	Afebrile	Slight stricture involving rectovaginal sep- tum; ruptured Bartholin abscess at de- livery.
30. S. M. 1942	20	1-0-1-0-1	14	4-38		Vertex spontaneous	4,120	Afebrile	Stricture of variable extent; slight at de- livery.
31. G. B.	39	2-2-0-0-2	145	34-15		Operative low forceps	3,240	Endometritis	Slight stricture; dystocia due to kypho- scoliosis, asynclitism and maternal ex- haustion.

Note: Duration of second stage is recorded in minutes. Duration of total labor is recorded in hours and minutes. Fetal weight is recorded in grams.

Parity as recorded in this table includes all pregnancies. Parity as referred to in the body of this report excludes abortions not observed at the Johns Hopkins Hospital. A patient with no previous term or premature deliveries is considered an essential primipara.

midable obstacle despite its patency. When this last condition exists, pelvic delivery may be possible only if some tearing occurs. The most dramatic form of this tearing, and one which, at the moment, provides the only recognizable clinical syndrome, is rupture of the rectum into the peritoneal cavity.

Of course, it is not possible to rule out the chance that the rectum may rupture within the pelvic floor, or that the necessary additional space may be provided by tears in the connective tissue without involving any hollow viscus. When the scarring is low and involves the rectovaginal septum, perineal laceration may also occur. When the scarring is high, episiotomy or perineal tear can only slightly release the tension created by higher scar tissue, and, under these circumstances, the obstruction may be such that the uterus may rupture.

As has been discussed above, thirty labors in the presence of rectal stricture are recorded in the literature, with a total of seven deaths, a mortality of 23 per cent.

It must be emphasized that the majority of reports are concerned with isolated maternal fatalities. Only one extensive series of cases is to be found, that of Kassebohm and Schreiber from Harlem Hospital in New York, including eighteen labors with two maternal deaths. The apparent high mortality rate in labor which appears in the literature is therefore clearly the result of a high degree of selection of the available data.

The cause of death in five cases was made clear by autopsy in four and operation in one (Cases 1, 2, 4, 21 and 30, Table I). In another, examination of the birth canal showed it to be intact and the early post-partum death must therefore be attributed to rupture of the rectum (Case 24, Table I). Information about the last case is too meager to allow any conclusions (Case 3, Table I). There are therefore five cases of rupture of the rectum recorded in seventy-eight labors associated with rectal stricture, forty-eight of these being added by this paper. The fact that the incidence of rupture of the rectum in the series of forty-eight labors at the Johns Hopkins hospital is zero and that the literature is highly selective makes it seem likely that the rate heretofore reported is excessive.

Two cases of ruptured uterus have occurred (Case 21, Table I; Case 10, Table IV). Anderson's case was associated with version and extraction and the etiology of the rupture is therefore uncertain. The one case of ruptured uterus in our series did not occur under direct observation and accordingly is also of uncertain etiology. In a search for further evidence as to the possible etiologic relation of rectal stricture to ruptured uterus, all cases of ruptured uterus at the Johns Hopkins hospital were reviewed and no further instance of rectal stricture found.

The therapeutic recommendations of the reports in the literature are therapeutic abortion, early gastrointestinal surgery, cesarean section or pelvic delivery with wide episiotomy, and routine sterilization.

The major objection to these proposed solutions is that they provide for no individualization of the treatment of the patient. On this ground alone, as will be discussed later, abortion, section and sterilization cannot be proposed for every patient with a rectal stricture.

Intestinal surgery is most appropriately reserved for treatment of the complications of the stricture itself. Moreover, colostomy in no way alters the scar tissue in the pelvis, which is responsible for dystocia.

Nor does wide or bilateral episiotomy solve the problem, since it does not create space where the tension which ruptures the rectum probably exerts its full force. Once the vertex has reached the outlet, its greatest diameter has passed the area of maximum cicatrization. Episiotomy, while it is undoubtedly of value in lessening the soft-tissue tension at delivery, is therefore best employed as the individual case demands, and for the customary indications.

The policy of the department of obstetrics of the Johns Hopkins hospital in the handling of patients with rectal stricture has been in the process of formation since the recent reports of fatality due to rupture of the rectum. Its basis has been a consideration of each patient in terms of the extent of the rectal pathology.

Involvement of the pouch of Douglas by the pelvic scarring, regardless of the caliber of the stricture or the state of the rectovaginal septum, is felt to carry with it the greatest risk of rupture of the rectum, and cesarean section is advised. Scarring of the rectovaginal septum and the presence of rectovaginal fistula appear less grave, and the decision in regard to cesarean section depends on parity, the state of the pelvis, the history of previous bowel obstruction and other potential causes of dystocia. Stricture of the rectum in which all scarring is limited to the rectal wall, and especially where the stricture is high and out of the pelvis, is not thought to be a bar to pelvic delivery.

Each patient is seen in a consultation clinic with the chief of the obstetric service as early as possible in pregnancy and again at about thirty-two weeks, for re-examination. An active process may advance considerably during pregnancy so that the choice of means of delivery is altered. Contrariwise, the scarring may be softened to such a degree that pelvic delivery is felt to be without hazard, even though cesarean section was previously decided upon.

Existence of a colostomy generally acts as a deterrent from cesarean section because of the potential difficulties of any transperitoneal procedure after colostomy.

Pelvic delivery in the presence of enterostomy seems to be a safe procedure on the basis of the limited experience in this clinic. In addition to the two patients with colostomy described above, one patient,

not included in this series, has been observed with an ileostomy performed for ulcerative colitis. She was delivered of her first pregnancy by elective low forceps after 13 hours of labor. Whether the occurrence of uterine inertia in both patients with colostomy and rectal stricture was more than coincidence cannot be determined now. In these three cases the function of the enterostomies was in no wise disturbed by pelvic delivery; the three infants all did well, and the mothers' puerperia were uneventful.

If a patient suffers obstruction near term which fails to respond to nonoperative treatment, cesarean section is combined with colostomy. If cesarean section is performed electively, it is felt advisable to establish a precolostomy at the same time. In this operation, a segment of the descending colon is brought through a left lower quadrant gridiron incision in the fascia and muscle and sutured so that it lies directly under the skin, without interrupting its continuity. Should obstruction occur at a later date, a functioning colostomy may be established by a simple incision through the skin and subjacent bowel wall without entering the peritoneal cavity. The precolostomy may be performed by a consulting surgeon, adds little to the operating time and, since it is a closed and aseptic procedure, does not add to postoperative morbidity.

The patients chosen for pelvic delivery require special attention. Spontaneous delivery is preferred on the ground that the natural forces of labor are less likely to tear the scarred tissues than is forceps delivery.

Prolongation of the second stage of labor while the mother and fetus remain in good condition is regarded as a smaller risk than operative interference. Heavy sedation in labor is to be avoided, since it may mask the distinctive clinical picture of rupture of the rectum, the earliest symptom of which may be severe lower abdominal pain.

It has been proposed that these patients be prepared for pelvic delivery with a bowel antiseptic such as succinylsulfathiazole to minimize the danger of peritonitis following rupture of the rectum. However, once rupture occurs, the safety of the patient inevitably depends on the immediate recognition of the clinical picture and immediate operation.

It is felt that pelvic deliveries in the presence of rectal stricture should be limited in number, especially if the disease is progressing. For this reason post-partum tubal sterilization may be offered to the patient.

Stricture of the rectum is an unusual and grave complication of labor, and one not likely to decrease in incidence in the visible future. It is therefore incumbent upon obstetricians, particularly in the large clinics serving Negro patients, to bend every effort toward the early accumulation of information and the evolution of a program for the safe management of pregnancy complicated by this condition.

Summary

Forty-eight labors in the presence of rectal stricture observed by the department of obstetrics of the Johns Hopkins hospital are reported. The incidence of grave complications is found to be lower than that previously reported in the literature. One maternal death due to rupture of the uterus apparently unconnected with rectal stricture occurred in this series, and there was no obvious instance of rupture of the rectum.

The program evolved by this department for the management of these patients in labor depends primarily on a consideration of the location and extent of the rectal scarring in the individual patient. Cesarean section is reserved for those patients with extensive involvement of the pouch of Douglas or the pelvic soft parts. Colostomy or precolostomy may be performed in association with cesarean section if necessary. Pre-existing colostomy is not felt to be a bar to pelvic delivery. Spontaneous delivery and avoidance of sedation are advised if pelvic delivery is decided upon, and the patient must be watched closely post partum for the appearance of signs and symptoms of rupture of the rectum.

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The roentgen ray studies of the authors have shown them that the fetus in utero does not normally assume the ball-like attitude as is generally believed. In fact, many bizarre attitudes were observed. In polyhydramnios the upper and lower extremities are found distant from the trunk as in a swimmer's attitude. If, in addition to this attitude, there is hyperextension of the cervical spinal column, one should suspect polyhydramnion and hydrops of the fetus. The authors believe that occasionally x-ray studies may reveal an abnormal attitude which would indicate induction of labor or embryotomy, thereby avoiding an unnecessary operation such as cesarean section.

ECTOPIC PREGNANCY

A Review of 75 Consecutive Cases as Compared With a Previous Review of 82 Cases*

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IN NOVEMBER, 1931, Scheffey, Stimson, and Morgan,¹ in a report given before the Obstetrical Society of Philadelphia, presented an analysis of 82 consecutive cases of ectopic pregnancy as observed in the gynecologic ward service at Jefferson Medical College Hospital between September 1, 1921 and September 1, 1931. In the eleven-year period from September 1, 1931 to September 1, 1942, there occurred 75 additional ectopic pregnancies on the same service. In this report, we shall analyze the salient features of these additional cases, and correlate our findings with the previous series.

Incidence, Age, and Reproductive History

The seventy-five ectopic pregnancies reviewed in this report occurred among 5,579 admissions, representing an incidence of 1.3 per cent, as compared with the previous incidence of 2.1 per cent. Both Farrar² and Urdan³ reported an incidence of 1.5 per cent among gynecologic patients.

The ages of these patients ranged from 18 to 44 years. The largest number of patients, forty-four (58 per cent), were in their third decade (21 to 30 years), a percentage identical with that noted in the first series. This finding agrees closely with that of other observers: Johnson,⁴ 57 per cent; Ware and Wenn,⁵ 56 per cent; Schauffler,⁶ 50 per cent.

TABLE I. AGE INCIDENCE

Under 21 years	4	5 per cent
21 to 30 years	44	58 per cent
31 to 40 years	24	32 per cent
Over 40 years	3	4 per cent

The reproductive history of these patients is pertinent. Twelve patients (16 per cent), had never conceived before. Thirteen patients (17 per cent), had conceived but the pregnancies had not continued to term, twelve having terminated in abortions with one resulting in an ectopic pregnancy. Thus, significantly, 33 per cent of the patients had not conceived previously, or having conceived did not carry any pregnancies to term. In the previous series, a similar condition was found in 29 per cent. This indicates a relative infertility in the patients reviewed in this study.

Etiology

Many reasons have been ascribed as causative of extrauterine pregnancy. Novak⁷ divides these into two main groups: one, factors which

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delay or prevent the passage of the fertilized ovum to the uterine cavity; two, factors which increase the receptiveness of the tubal mucosa for implantation of the fertilized ovum.

The most frequent factor that delays the passage of the fertilized ovum is an obstruction produced by inflammatory changes in the tube itself. This theory was advanced by Lawson Tait⁸ in 1888. Hecker,⁹ as early as 1859, called attention to the fact that peritoneal adhesions, by compressing the lumen of the tube, may interfere with the passage of the ovum. Conceivably, pelvic enlargements may cause a constriction of the tube because of external pressure.

In thirty patients (40 per cent), gross evidence of chronic inflammatory change in the uninvolved tube was found at operation. Hence, it is probable that like changes may have been present in a similar percentage of the tubes in which the ectopic pregnancy occurred. This incidence corresponds exactly to the figure in the previous survey. In one case an acute salpingitis coexisted with the ectopic pregnancy. Fibromyoma uteri were present in four patients, and in one instance, the fibromyoma surrounded the tube at the cornua.

Twenty patients (26 per cent), approximately the same figure noted in our former study, had had previous abdominal operations. Five in the former, and three in the second series, had been operated upon for ectopic pregnancy (5 per cent of 157 cases). Thus the possibility of postoperative adhesions involving the tubes must be borne in mind as an etiologic factor in the occurrence of extrauterine pregnancy.

Novak⁷ explains further why the fertilized ovum does not lodge in the tubes normally. First, the trophoblast is not developed until the fertilized ovum reaches the uterine cavity; second, the tubal mucosa is not designed for implantation. He believes that the retardation of the progress of the ovum gives time for the development of the trophoblast while the fertilized ovum is still in the tube. Evidence in support of the theory that receptivity of the tubal mucosa to the fertilized ovum has been increased is found in the fact that a definite decidual reaction was found in twenty-seven (36 per cent), of the removed specimens examined histologically. This phase was not considered in the previous study.

Symptomatology

The two most common complaints were abdominal pain and vaginal bleeding. Every patient experienced pain at some time. The date of onset of abdominal pain in relation to the last menstrual period was as follows: In twelve patients (16 per cent), between 2 and 4 weeks after the last regular period; in thirty-three patients (44 per cent), between 4 and 6 weeks; in twenty-six patients (34 per cent), between 6 and 8 weeks; and in four patients (5 per cent), between 8 and 12 weeks.

Forty-nine patients (65 per cent), complained of severe and persistent pain. The remainder described their pain as being "colicky" or intermittent. In ten instances, the pain was referred to the bladder or rectum. Upper abdominal pain was mentioned only once. As a rule, the discomfort was generalized in distribution, only one-third of the patients localizing the pain in one or the other lower quadrant. Pain was also a constant symptom in the previous series; in 56 per cent of the patients, it was severe or lancinating and in the remainder relatively moderate.

The menstrual history prior to the occurrence of the present illness was normal in sixty-seven patients (90 per cent), and irregular in periodicity in only eight patients. This finding indicates that in the majority of patients there is no association between the normalcy of the menstrual function and the occurrence of an ectopic pregnancy, an observation similar to that noted in our previous survey.

Vaginal bleeding of an irregular nature subsequent to the last previous regular menstrual period was present in seventy patients (93 per cent). Five patients gave no history of any external bleeding since the previous regular period.

Sampson¹⁰ established the endometrium as the source of the external bleeding in ectopic pregnancy, and believes that the bleeding is initiated by the separation of the decidua, following the death of the embryo. This is a popular point of view, the physiology of which has been painstakingly explained by Jones and Brewer.¹¹ In nineteen patients (25 per cent), the bleeding occurred before the next expected menstrual period and in fifty-one patients (68 per cent), at the time of or after the expected menses.

In analyzing the time of bleeding in relation to the findings at operation, one is forcibly impressed by the following observation: Whereas twelve (63 per cent), of the patients with tubal rupture bled before the expected period, only seven (13 per cent), of those with tubal abortion or intact ectopic pregnancy bled before the expected menses. Thus, in this series, we found that the majority of the tubal ruptures had external vaginal bleeding before the expected menses and that the majority of the tubal abortions and intact ectopic pregnancies gave a history of a "missed" period. (Table II.)

TABLE II. EXTERNAL BLEEDING IN RELATION TO OPERATIVE FINDINGS

RELATIONSHIP OF BLEEDING TO MENSES	TUBAL RUPTURE	TUBAL ABORTION	INTACT ECTOPIC
Prior	12	5	2
During or after	4	33	14
No bleeding	3	2	0
	19	40	16

Syncope, usually mentioned as one of the cardinal symptoms, occurred in thirteen patients (17 per cent). Eight of these patients had ruptured tubal pregnancies. In the previous series, syncope was present in 27 per cent of the patients.

The concomitant signs of pregnancy were relatively unreliable. Only five patients had any symptoms referable to the breasts while eleven complained of nausea.

Physical Findings

Physical examination revealed abdominal tenderness either general or localized in seventy patients (93 per cent). In the previous series, the figure was 85 per cent. Rigidity was found in fourteen (19 per cent). In four patients, abdominal masses could be palpated, and abdominal distension was noted in ten (13 per cent).

Pelvic examination was carried out in all but two of the patients. The most constant sign was adnexal tenderness which was present in fifty-eight (77 per cent). Definite pelvic masses were palpable in forty-four (59 per cent). A softened cervix was found 18 times, and a

palpably enlarged uterini in 22 instances (29 per cent). These findings correspond closely to those of the previous analysis.

Repeated blood pressure readings were valuable in cases where progressive internal hemorrhage was suspected. In the majority of patients the blood pressure was well maintained. Only sixteen patients (21 per cent), had systolic pressures below 100 mm. of mercury; nine of these had ruptured tubes.

The pulse rate was significant in cases of tubal rupture; of the seventeen patients having a pulse rate over 110, eleven had tubal ruptures. The patients' temperature upon admission was of little diagnostic value, the majority ranging between 98 and 100 degrees. Seven had temperatures over 100, and all of these were found to have a considerable amount of free blood in the peritoneal cavity. Two patients who were admitted in shock because of tubal rupture had temperatures below 98 degrees.

Blood Studies

The blood findings assume more significance when reviewed in relation to operative findings. Of the five patients having red cell counts under 2.5 million, four had ruptured tubes. Only one patient with a tubal abortion and none with an intact tubal pregnancy had a red cell count under 2.5 million. Hemoglobin readings generally corresponded to the red cell values. Evidence of hemoconcentration was not noted.

Leucocytosis appears with intra-abdominal hemorrhage and is in response to peritoneal irritation. In this series, white cell counts over 15,000 were found in fifteen patients with tubal rupture and in three with tubal abortions. Counts under 15,000 were found in thirty-seven patients with tubal abortion and in all with intact ectopic pregnancy. Thus very high leucocyte counts were relatively more frequent with rupture than with tubal abortions. Where the pregnancy was intact, the leucocyte count was nearly always under 10,000. These findings correspond to those reported by Ricci,¹² and are similar to those found in the earlier review.

The blood sedimentation rate was increased in cases where free blood was found in the pelvis. The most rapid sedimentation rates (Cutler Method) occurred in the patients having tubal ruptures and tubal abortions. In the intact ectopic pregnancies, only one showed a rate greater than 20 mm. in 2 hours. This interpretation is in accord with previous observations, and leads to the conclusion that the sedimentation rate is a fairly accurate indicator of intra-abdominal hemorrhage. Its greatest value is in differentiating pelvic inflammatory disease from an intact tubal pregnancy; when inflammatory changes following rupture or abortion have occurred, its differential significance is correspondingly decreased. (Table III.)

Accessory Diagnostic Procedures

Accessory diagnostic procedures performed included the biologic test for pregnancy and peritoneoscopy. Endometrial curettage was carried out frequently, but chiefly as a matter of record.

Biologic tests may give either positive or negative results depending upon whether or not the trophoblast is still functionally active in the production of chorionic gonadotropic hormones. With death of the fetus and degeneration of the chorionic villi, the elaboration of hormones ceases and the test becomes negative.

TABLE III. BLOOD STUDIES

HEMOGLOBIN	OVER 80 PER CENT	55 TO 80 PER CENT	LESS THAN 55 PER CENT
Tubal rupture	2	9	8
Tubal abortion	12	27	1
Intact ectopic	5	11	0
	19 (25 per cent)	47 (63 per cent)	9 (12 per cent)
RED BLOOD CELLS	OVER 4 MILLION	2.5 TO 4.0 MILLION	LESS THAN 2.5 MILLION
Tubal rupture	2	13	4
Tubal abortion	12	27	1
Intact ectopic	5	11	0
	19 (25 per cent)	51 (67 per cent)	5 (7 per cent)
WHITE BLOOD CELLS	5 TO 10 THOUSAND	10 TO 15 THOUSAND	OVER 15 THOUSAND
Tubal rupture	2	2	15
Tubal abortion	23	14	3
Intact ectopic	14	2	0
	39 (52 per cent)	18 (24 per cent)	18 (24 per cent)
BLOOD SEDIMENTATION	5 TO 12 MM	12 TO 20 MM	OVER 20 MM
Tubal rupture	1	4	11
Tubal abortion	4	11	22
Intact ectopic	4	4	1
	9 (12 per cent)	19 (25 per cent)	34 (45 per cent)

The Friedman test was carried out in thirty-one patients; twenty-two (71 per cent), were positive and nine (29 per cent), were negative. In the twenty-two positive tests, the Friedman test was of distinct value, for in nine of these patients the diagnosis was not definitely made until the positive test was obtained. The presumptive diagnoses in these nine patients were pelvic inflammatory disease, four cases; ureteral stricture, one case; infected abortion, three cases; pelvic abscess, one case. In the remaining thirteen cases, the diagnosis of ectopic pregnancy was made before the results were known, and the tests were therefore confirmatory.

The preoperative diagnoses in nine patients having negative tests were ectopic pregnancy, five patients; chronic pelvic inflammatory disease, two patients; pelvic abscess, one patient; fibromyoma uteri, one patient. The operative findings in these patients showed five "old" tubal pregnancies with much organized blood clot in the pelvis; three fairly recent tubal abortions, and one patient had an intact tubal pregnancy.

The Friedman test was certainly of value in a group of twenty-nine patients in whom ectopic pregnancy was suspected. Seventeen of them responded negatively, and the final diagnoses were: pelvic inflammatory disease, thirteen; functional uterine bleeding, 2; incomplete abortion, two. The remaining twelve patients, had positive tests. Of these, ten had intrauterine pregnancies, while in two instances, the test was false; for the patients had pelvic inflammatory disease, proved in one case by operation and in the other by clinical means. In the earlier series only two biologic tests were performed.

Curettage was performed prior to laparotomy in twenty-two patients, showing a decidual reaction 9 times; an interval endometrium,

9 times; a premenstrual endometrium, 2 times, a postmenstrual endometrium, 1 time; a local endometrial hyperplasia, 1 time. The presence of a nondecidual reaction in thirteen patients may be explained on the basis of the death of the embryo, whereby the decidua had been cast off, after which various phases of the endometrial picture returned. These findings are in accord with the recent observations of Siddal and Jarvis¹³ who state that "a uterine curettage is a valuable diagnostic aid" and that "the finding of intact decidua without chorionic villi is strong presumptive evidence of extra-uterine pregnancy." "The absence of decidual reaction is not reliable evidence against ectopic pregnancy."

Eleven patients in this series had both curettage and a Friedman test performed. In seven of these, the Friedman test was positive, and there was a decidual reaction in the endometrium as well. In two patients, the biologic test was negative, and there was no decidual reaction present. In two other patients in whom the biologic test was negative, a decidual reaction was present, thus demonstrating that the Friedman test was false in these instances. These latter results are at variance with the recent statement of Goldblatt and Schwartz¹⁴ who concluded in their studies correlating the Friedman test with the endometrial picture that "no patient with uterine decidua had a negative Friedman test, and no patient with a negative Friedman test had uterine decidua at the time of curettage."

Peritoneoscopy was a useful diagnostic aid in five patients. The finding of free blood in the peritoneal cavity and the visualization of an adnexal mass confirmed the diagnosis once and operation immediately followed the procedure. In the remaining four patients in whom ectopic pregnancy was suspected, the procedure revealed cystic ovaries in two instances, pelvic inflammatory disease in another, and an intra-uterine pregnancy in the fourth case.

Posterior colpotomy was not performed for diagnosis in any of our cases.

Diagnosis

Correct preoperative diagnoses of ectopic pregnancy were confirmed at operation in 54 of the 75 patients in the series (72 per cent). The diagnoses were incorrect in the case of 21 remaining patients (28 per cent), in whom the following conditions were diagnosed preoperatively: pelvic inflammatory disease, 5; incomplete abortion, 4; intrauterine pregnancy, 3; retroversion of the uterus, 3; ovarian cysts, 3; pelvic abscess, 1; ureteral stricture and ovarian cyst, 1; intrauterine and intestinal obstruction, 1.

During the same eleven-year period, 13 patients diagnosed as ectopic pregnancies, were found upon laparotomy to have: pelvic inflammatory disease, 4; ruptured Graafian follicle, 2; tuboovarian abscess, 1; myoma and intrauterine pregnancy, 1; dermoid cyst, and intrauterine pregnancy, 1; ovarian cyst and intrauterine pregnancy, 1; ovarian cyst and twisted pedicle, 1; ruptured appendix, 1; no pathology, 1.

The most frequent error encountered in diagnosis was due to the confusion that exists between pelvic inflammatory disease and ectopic pregnancy. Ovarian cysts, accompanying an intrauterine pregnancy, and ruptured Graafian follicle cysts occurred next in frequency. The 1921 to 1931 series showed a correct preoperative diagnosis in 78 per cent of the patients. Here, too, pelvic inflammatory disease was most frequently mistaken for ectopic pregnancy.

In patients operated upon immediately or within 24 hours after admission to the ward, the symptoms and signs were so clear-cut and urgent that no difficulty was encountered in making a diagnosis. Of the 75 patients here reported, 38 were operated upon within 24 hours and the diagnosis of ectopic pregnancy was verified in each. Of the 8 patients operated upon within 24 to 72 hours, the preoperative diagnosis of ectopic pregnancy was made in six. Of the 29 patients operated upon after 72 hours, 10 were correctly diagnosed preoperatively. That the greatest number of incorrect diagnosis would be in the delayed cases, is understandable. Here the findings were not clear and operation was delayed as a matter of judgment. (Table IV.)

TABLE IV. DIAGNOSIS

DIAGNOSIS	OPERATED UPON WITHIN 24 HOURS		OPERATED UPON WITH- IN 24 TO 72 HOURS		OPERATED UPON AFTER 72 HOURS	
	CORRECT	INCORRECT	CORRECT	INCORRECT	CORRECT	INCORRECT
Tubal rupture	15	0	0	0	1	3
Tubal abortion	20	0	2	2	5	11
Intact ectopic	3	0	4	0	4	5

It is of interest to note that 107 patients were sent to the ward service with a presumptive diagnosis of ectopic pregnancy. After sufficient observation, the attending staff made a diagnosis of ectopic pregnancy in 67 of them, and they were all operated upon. Fifty-four (80 per cent), were found to have extrauterine pregnancies. Thus of all patients sent to the ward with an admitting diagnosis of ectopic pregnancy, 50 per cent were eventually proved to have this condition.

Operative Findings

The operative findings in this series were as follows: tubal rupture, 19 patients (25 per cent); tubal abortion, 40 patients (53 per cent); intact tubal pregnancy, 15 patients (20 per cent); ovarian pregnancy, 1 patient (1 per cent).

This represents a ratio of 2 tubal abortions to 1 tubal rupture.

In comparing these findings with the previous analysis, considerable variance is found—a reversal of this proportion, viz., 3 tubal ruptures to 1 tubal abortion. The previous report showed: tubal ruptures, 66 per cent; tubal abortions, 19 per cent; intact tubal pregnancy, 14 per cent. This difference may be explained by more careful recording of the lesions observed in the present series, and throws doubt on the accuracy of the former estimate.

The ectopic pregnancy occurred on the right side in 40 patients, on the left side in 35 patients, a finding of no particular significance, as in the previous study.

At laparotomy, free blood was found in the peritoneal cavity of 63 patients, and in 16 instances the amount was large. In 7 no free blood was noted. As previously noted, gross chronic inflammatory changes were found in the uninvolved tube in 40 per cent of both series.

An associated uterine abnormality was found 20 times (26 per cent), as follows: fibromyoma, 4 cases; retroflexio-version, 8; endometriosis, 1; uterus adherent to tubes, 6; uterus adherent to old cesarian scar, 1. In the previous analysis, the uterine abnormalities amounted to 8.5 per cent.

Operative Treatment

Whenever possible, conservatism was practiced. For brevity, the operative procedures are outlined in Table V.

TABLE V. OPERATIVE TREATMENT

Unilateral Salpingectomy	31
Curettage and Unilateral Salpingectomy	8
Curettage and Salpingo-Oophorectomy	3
Salpingo-Oophorectomy	13
Drainage and Curettage, Cauterization of Cervix and Salpingo-Oophorectomy	2
Drainage and Curettage, Cauterization of Cervix and Salpingectomy	1
Salpingo-Oophorectomy and Appendectomy	3
Salpingectomy and Appendectomy	3
Drainage and Curettage, Colporrhaphy, Salpingectomy and Appendectomy	1
Drainage and Curettage, Trachelectomy, Colporrhaphy and Salpingectomy	1
Salpingectomy, Appendectomy and Tubal Ligation	1
Curettage, Cauterization of Cervix and Bilateral Salpingectomy	1
Curettage, Bilateral Salpingo-Oophorectomy	2
Drainage and Curettage, Bilateral Salpingo-Oophorectomy and Hysterectomy	2
Bilateral Salpingo-Oophorectomy and Hysterectomy	2
Curettage, Removal of Fetus From Cul-De-Sac and Suspension of Uterus	1

Sixty-six of the 75 patients in this series were not rendered sterile. In 27 of these, the reproductive history was followed to date. Only five conceived; 2 had miscarriages; 2 had a second ectopic; 1 carried the pregnancy to term.

Morbidity and Mortality

Six patients (8 per cent), had a complicated postoperative course. The nature of these complications and the postoperative residence is as follows: one, infected incision, 61 days; one, cystitis, 29 days; two, atelectasis, 18 days and 16 days; one, pneumonia, 28 days; one, phlebitis, 36 days.

One death occurred in this series. a mortality rate of 1.3 per cent. This patient was operated upon immediately after admission to the ward following a delay of several hours in the receiving ward. Death occurred on the fourth postoperative day, despite all attempts to combat initial shock and hemorrhage. The autopsy findings were fibromyoma uteri, congestion of the spleen, and parenchymatous degeneration of both kidneys.

In the previous series there were 4 deaths, a total mortality of 4.8 per cent. Two patients were moribund on admission and died before operation could be performed. There were 2 postoperative deaths, and operative mortality of 2.5 per cent. The combined mortality for the two series includes 5 deaths (3.2 per cent), and an operative mortality of 3 deaths (1.9 per cent).

Summary

A series of 75 consecutive cases of ectopic pregnancy was analyzed and compared with a previous review of 82 cases. The incidence

among gynecologic admissions was 1.3 per cent in this series and 1.6 per cent in the combined review. In both studies the majority of patients were in the third decade of life.

One-third of the patients had either not conceived previously, or, having conceived, did not carry the pregnancy to term.

Gross evidence of chronic inflammatory change in the uninvolved tube was found in 40 per cent of the patients, and 26 per cent had had previous abdominal operations. This high incidence of inflammatory disease and the role that postoperative adhesions may play in causing mechanical hindrance, are important etiologic factors in the production of an ectopic gestation.

Abdominal pain was experienced by all patients and the onset was most frequently observed from 2 to 4 weeks after the last previous period.

Some form of irregularity of the current menstrual cycle was noted in 93 per cent of the patients. The majority of those experiencing tubal rupture reported external vaginal bleeding before the expected menses, while the majority with tubal abortions and intact ectopic pregnancies gave a history of a "missed period."

Concomitant signs of pregnancy were infrequent.

Pelvic masses were palpable in 59 per cent of the patients.

In intact tubal pregnancy, blood studies are comparatively normal. As tubal abortion or tubal rupture occurs, the red cell count decreases, leucocytosis increases, and the sedimentation rate becomes more rapid.

The biologic test can be a distinct aid in diagnosis, but only when supported by other signs and symptoms of ectopic pregnancy.

In nine of the 22 patients in whom a uterine curettage was done, a decidual reaction of the endometrium was observed.

Peritoneoscopy is a rational procedure and has much to offer in the confusing case.

The proportion of tubal abortion to tubal rupture was 2 to 1; this is a reversal of the proportion recorded in the previous review.

Correct diagnoses were made in 76 per cent of the combined series. Pelvic inflammatory disease was the lesion most frequently confused with ectopic pregnancy.

The total mortality rate in the combined series amounted to 3.2 per cent, while the operative mortality rate was 1.9 per cent. For the first series, the operative mortality rate was 2.5 per cent, and for the present series 1.3 per cent.

The deaths in both series emphasize the danger of delayed operation in tubal pregnancy. Prompt operation, and the use of blood transfusion and plasma to combat hemorrhage and shock, are efficacious means for decreasing the mortality rate.

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1831 DELANCEY STREET
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THE INTRINSIC RISK OF BREECH DELIVERY

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OBSTETRIC statistics invariably show a high fetal mortality for the "breech baby"; therefore, it is usually assumed that breech delivery is extremely dangerous. The fetal hazard probably has been exaggerated in the minds of obstetricians by failure to distinguish between the risks of *breech presentation* and the risks of *breech delivery*. Breech presentation occurs often in premature labors and in cases of gross fetal anomalies and it is not infrequently complicated by placenta previa or prolapsed cord. These factors constitute hazards which should be distinguished from the intrinsic risk of the delivery. It is the purpose of this study to discover, if possible, the fetal mortality attendant upon uncomplicated breech delivery.

Because breech presentations occur not much more often than four times in 100 deliveries, it is unlikely that a single obstetrician will be able to submit a series of personally attended cases large enough to have statistic significance. Therefore, deductions must be based upon a series of cases delivered by a group of obstetricians. Many clinics have presented data on large numbers of breech deliveries, but these large series usually include deliveries made by interns, residents, courtesy members of the staff and others of undetermined experience and competence. For these reasons the massed data previously published do not indicate what fetal mortality may be expected in uncomplicated breech deliveries under ideal conditions. This study is an analysis of a series of cases which, from the standpoint of obstetric management, approaches ideal conditions and from the standpoint of the statistician is otherwise unselected.

Since there is no satisfactory definition of an "expert obstetrician," we have arbitrarily decided to regard certification by the American Board of Obstetrics and Gynecology as acceptable evidence of competence. In the 1942 edition of the *Directory of Medical Specialists* (Columbia Press) 17 members of the Staff of the Pennsylvania Hospital (Philadelphia Lying-in) are listed as obstetricians. From some 1400 records of breech presentation in the Pennsylvania Hospital we selected *every case personally delivered* by these 17 obstetricians after their certification by the Board. Cases delivered by others under supervision by these men, or in consultation with them, are not included. (Table I.) This somewhat artificial standard has several disadvantages: it greatly reduces the number of cases available for study, it takes no account of results obtained by some older and several younger staff members of unquestioned ability, and, in several instances, it places personal responsibility upon a chief or junior attending obstetrician who was called to the delivery room in an emergency for which he was not accountable. On the other hand, such a completely arbitrary standard renders the data suitable for comparison.

Two hundred and eleven cases of breech presentation personally delivered by these 17 obstetricians are the basis of this study. One hundred and eighty babies were delivered vaginally; internal podalic versions were excluded from the series. Thirty-one patients, all with single pregnancies, were delivered by cesarean section. The number seems large (14 per cent of the breech cases) but is explained in Table II. Our special interest was directed to the group in which cesarean section was employed because of "disproportion," for we

TABLE I. SHOWING THE NUMBER OF STAFF MEMBERS OF THE PHILADELPHIA LYING-IN HOSPITAL CERTIFIED BY THE AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, THE YEAR OF CERTIFICATION, AND THE RESPECTIVE NUMBERS OF BREECH DELIVERIES BY THEM SINCE CERTIFICATION

DOC- TOR	YEAR CERTI- FIED	BEFORE 1933	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	TOTAL
1	1930	0	1	0	4	4	1	0	2	2	5	5	24
2	1930	0	0	0	0	0	0	0	0	0	0	0	0
3	1931	0	0	0	0	0	0	1	0	0	0	0	1
4	1931	0	3	2	3	8	7	6	6	6	2	3	46
5	1931	0	1	0	0	0	0	0	0	0	0	0	1
6	1934	-	-	0	0	2	2	0	0	0	5	0	9
7	1936	-	-	-	-	6	10	6	7	8	9	14	60
8	1937	-	-	-	-	-	0	2	3	0	3	0	8
9	1937	-	-	-	-	-	0	0	1	1	1	0	3
10	1937	-	-	-	-	-	2	0	4	2	4	0	12
11	1938	-	-	-	-	-	-	7	5	5	4	0	21
12	1939	-	-	-	-	-	-	-	0	0	0	0	0
13	1939	-	-	-	-	-	-	-	1	0	5	3	9
14	1940	-	-	-	-	-	-	-	-	3	3	6	12
15	1940	-	-	-	-	-	-	-	-	0	0	0	0
16	1940	-	-	-	-	-	-	-	-	2	1	1	4
17	1941	-	-	-	-	-	-	-	-	-	1	0	1
Total breech deliveries		0	5	2	7	20	22	22	29	29	43	32	211

felt that these were the patients whose babies might have been lost if vaginal delivery had been attempted. Although it is often impossible to determine from an old history whether cesarean section was or was not indicated, Table III provides justification for the procedure in most instances. In 15 of the 17 cases of disproportion x-ray studies of the pelvis contributed to the decision on operation.

Of the 211 infants delivered, 189 left the hospital alive and well; 22 died. The causes of death are shown in Table IV. Table V gives the fetal mortality for the series. Premature and malformed fetuses are excluded for obvious reasons as is the case of death of the fetus from maternal toxemia four days ante partum. Since the presence of placenta previa introduces additional risk to the baby, such cases are excluded. It may be argued that twins, being small, do not run as

TABLE II. INDICATIONS FOR 31 CESAREAN SECTIONS IN A SERIES OF 211 BREECH PRESENTATIONS

Pelvic disproportion (see Table III)	17
Previous cesarean section	6
Placenta previa	3
Severe toxemia of pregnancy at 28 weeks	1*
Breech misdiagnosed as face presentation	1
Myoma uteri complicating breech presentation	1
Nullipara, aged 41, overdue one week	1
Dense vulvoperineal scars (lymphopathia venereum ?)	1
Total	31

*Only fetal death in this group. Baby died four days before delivery.

TABLE III. INDICATIONS FOR CESAREAN SECTION IN 17 CASES OF BREECH PRESENTATIONS DESCRIBED AS "DISPROPORTION"

HISTORY NUMBER	AGE	PARITY	BABY'S WEIGHT	TRIAL OF LABOR	X-RAY OF PELVIS	CONTRACTED PELVIS	REMARKS
27841	29	0	2982 Gm.	no	yes	yes	Android pelvis, overdue 1 wk.
23715	30	0	3098 Gm.	35 hr.	yes	yes	
23957	35	0	3204 Gm.	no	yes	yes	
17480	26	0	3320 Gm.	3 hr.	yes	yes	
30001	27	0	3349 Gm.	no	yes	yes	Android pelvis
27171	32	0	3465 Gm.	no	yes	yes	
23776	24	0	3470 Gm.	no	yes	yes	Android pelvis
12526	29	0	3628 Gm.	no	yes	no	Overdue 1 wk.
13136	25	0	3715 Gm.	no	no	yes	
30715	24	0	3716 Gm.	13 hr.	yes	no	Overdue 1 wk.
23286	21	0	4005 Gm.	8 hr.	yes	yes	Android pelvis
23102	33	1	2866 Gm.	no	yes	yes	Asymmetric android pelvis
23994	28	1	3127 Gm.	no	yes	yes	
27046	32	1	3156 Gm.	no	no	no	Previous breech delivery with fracture of fetal femur and clavicle
29337	34	1	3523 Gm.	no	yes	yes	Android pelvis, mitral stenosis, overdue 1 wk.
25030	33	1	3628 Gm.	no	yes	no	Previous breech delivery, baby died
17353	40	1	3710 Gm.	no	yes	no	Maternal congenital dislocation of hip with marked pelvic inclination

great a risk in breech delivery as single larger babies; or it may be said that in the case of the second twin the way has been smoothed. Twins are therefore omitted on the ground that risks typical of breech delivery are not encountered. Finally, cesarean sections are excluded since these are not truly breech births. We are left with 146 uncom-

TABLE IV. CAUSE OF 22 FETAL DEATHS IN 211 BREECH PRESENTATIONS

Lines 1 through 10 Table V	DEATHS NOT ATTRIBUTABLE TO DELIVERY	18
	Prematurity (babies less than 1,500 Gm.)	13
	Gross abnormalities: 2 babies each with hydrocephalus and spina bifida	2
	Severe toxemia of pregnancy, fetal death 4 days before delivery. No labor. Cesarean section	1
	Erythroblastosis fetalis, death of a "second" twin after 28 hours	1
	Placenta previa with severe hemorrhage	1
Lines 11 through 15 Table V	DEATHS PROBABLY NOT ATTRIBUTABLE TO MANAGEMENT OF DELIVERY	2
	Prematurity (weight 1,525 Gm.). Private patient	1
	Cord around neck, fetal distress 2 hours before delivery, death one hour before delivery. Private patient	1
	DEATHS DIRECTLY ATTRIBUTABLE TO MANAGEMENT OF DELIVERY	2
	Unrecognized disproportion: 2 wks. overdue, 31 hour labor, fetal death 21 hours before delivery, impacted breech, baby weighed 3,250 Gm. Ward patient	1
	Unrecognized disproportion: contracted pelvis, 12 hour labor, difficult delivery, baby weighed 3,110 Gm. Autopsy showed cerebral hemorrhages. Ward patient	1

TABLE V. FETAL MORTALITY IN 211 CASES OF BREECH PRESENTATION

LINE	CASES	FETAL DEATHS	FETAL MORTALITY
1 Breech presentations	211	22	10.4%
2 Babies less than 1,500 Gm.	15	13	—
3 —Remainder	196	9	4.6%
4 Gross abnormalities	2	2	—
5 —Remainder	194	7	3.6%
6 Severe toxemia of pregnancy, fetal death 4 days before labor or delivery	1	1	—
7 —Remainder	193	6	3.1%
8 Cases of placenta previa	6	1	—
9 —Remainder	187	5	2.6%
10 Breech presentation of second twin (one death from erythroblastosis fetalis)	8	1	—
11 —Remainder	179	4	2.2%
12 Breech presentation of first twin	6	0	—
13 —Remainder	173	4	2.3%
14 Cesarean section excluding 3 cesareans for placenta previa (included in line 8 above) and one for toxemia (included in line 6 above)	27	0	—
15 Breech presentations delivered vaginally excluding babies under 1,500 Gm., gross fetal abnormalities; one fetal death before the onset of labor, cases of placenta previa and twins	146*	4	2.7%

*The 146 cases shown in line 15 include 7 ward patients. Among these 7, two fetal deaths occurred. If ward patients are subtracted, the figures are 139 deliveries with 2 fetal deaths, or a fetal mortality of 1.4 per cent for private patients.

The low mortality rates are as much a credit to the pediatric as to the obstetric staff.

pliated breech deliveries; in these, four babies died. The fetal mortality rate of 2.7 per cent for this group represents, as nearly as can be determined, the intrinsic risk of breech delivery in this hospital. Even so, as Table IV makes clear, two of these four deaths could have been prevented, and, in retrospect, should have been prevented by cesarean section. There was no maternal mortality in the series.

In the management of breech presentation the following policies are recommended:

1. An x-ray study of the maternal pelvis should be made in nulliparous patients.

2. The membranes should seldom be ruptured artificially because of the danger of prolapse of the cord and the increased risk if cesarean section is subsequently necessary.

3. The patient should be fully anesthetized before delivery.

4. Decomposition of the breech is to be undertaken only in exceptional cases.

5. Traction is not to be used until the breech has passed the introitus.

6. In primiparas a generous episiotomy is advisable.

7. After delivery of the umbilicus the back should be turned uppermost to prevent posterior rotation of the occiput, and constant pressure should be maintained on the fetal head from above to prevent extension.

8. Forceps, preferably Piper's after-coming head forceps, should be utilized in all but the easiest cases.

9. Since there is no certain means of determining disproportion, consultation should be sought early in every doubtful case.

Summary

All breech deliveries attended by "certified" obstetricians at Pennsylvania Hospital have been studied to determine the risk inherent in breech delivery. After exclusion of babies of less than 1,500 Gm., cases of gross fetal abnormality, fetal death before the onset of labor, placenta previa, twin pregnancies, and babies delivered by cesarean section, there remain of the 211 breech presentations, 146 uncomplicated breech deliveries. Four of these 146 babies died, a mortality rate of 2.7 per cent. It therefore appears that breech delivery, in experienced hands, carries a lower fetal mortality rate than has heretofore been supposed.

The data permit a corollary statement: Further lowering of the gross fetal mortality rate in breech deliveries in this hospital depends not so much upon improving the technique of delivery as upon solving a much larger obstetrical problem, the prevention of premature labor.

GESTATIONAL NEURONITIS, A DEFICIENCY DISEASE*

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THE tendency of the obstetrician, or of any specialist, to regard his patients from the narrowed viewpoint of his particular field and to divorce from his specialty, whether by choice or by ignorance, well-recognized precepts of present-day internal medicine, is a deplorable one. In our discussion of this case of gestational neuronitis, we shall attempt to consider this failing in detail.

The term "cardiovascular collapse" is neither an adequate nor a scientific explanation of an infrequent, but all too common, cause of maternal morbidity and mortality. Neither the obstetrician nor the consulting internist need resort to complex, high sounding nomenclature when it is possible to define more precisely what the patient is suffering from, once an inquiry has been made into the etiological factors at work.

Case Report

C. M., a 25-year-old housewife, para 0, gravida 1, was admitted to the Bronx Hospital on October 10, 1940, six weeks before term, complaining of persistent vomiting of seven weeks' duration. Her family and past history were of no significance. Her diet during pregnancy had been well balanced, containing adequate amounts of fresh fruits, vegetables, meat and milk.

In the sixth month of gestation the patient began to suffer from marked nausea and tendency toward vomiting. The attacks of vomiting increased in frequency; during the seven weeks just previous to admission she had difficulty in retaining any nourishment. In the two weeks prior to admission her weight dropped from 161 to 151 pounds. She became relatively weak and could not perform her daily duties. There was some numbness of the lower extremities, but no pain, hyperesthesia or burning of the soles of the feet. The blood pressure rose slightly in the seventh month of pregnancy, from 120/70 to 134/80. The ankles swelled slightly. The urine showed a trace of albumin, but no sugar.

On admission, the patient presented the picture of a well-developed, fairly well-nourished female, not dyspneic, orthopneic or cyanotic. Her mentality was clear. The skin was dry, and there was some sealiness on the dorsum of the hands and feet and on the lower legs. The extraocular muscles were normal; the corneas were clear and the conjunctivas uninjected; examination of both fundi failed to reveal any abnormality. The nasal, buccal and pharyngeal mucous membranes appeared to be slightly thickened; they were dull red in color and sealy in certain areas. The dry, grayish pink tongue was covered with scales and was cracked in places. There was a slight acetone odor to the patient's breath. The respiratory rate was 22 per minute.

*Read before the Section of Obstetrics and Gynecology of the New York Academy of Medicine on October 28, 1941.

The point of maximum cardiac impulse was in the fifth intercostal space, 0.5 centimeter inside the midclavicular line. The sounds were of good quality at both apex and base, with no abnormal pulsations or thrills. A soft systolic blow, not transmitted, was heard at the pulmonary area. The ventricular and pulse rates were each 86 per minute and regular. Blood pressure was 120/80. Temperature was 100.6° F. Abdominal examination revealed a seven and one-half months' gestation. The fetal heart was heard in the right lower quadrant; the rate was 140, and the sounds were regular and of good quality. Rectal examination showed a hard, thick, closed cervix, with the head unengaged and the membranes intact. Neurologic examination was negative except for slight weakness and hypersensitivity. There was some tenderness, but no pain, in the leg muscles. Leg extension and leg raising were good. The superficial and deep reflexes were equal and active.

Laboratory data on admission were as follows: red blood cells 5,500,000, hemoglobin 90 per cent (Sahli), white blood cells 11,700, with a normal differential. Urinalysis was negative except for a four-plus acetoneuria. Carbon dioxide combining power was 30.5 c.c. per hundred cubic centimeters. Except for slightly elevated uric acid (6.3 milligrams per hundred cubic centimeters), the blood chemistry was within normal limits.

In view of the severe ketosis, as indicated by the low carbon dioxide combining power, acetoneuria and clinical evidence of dehydration, the patient was treated with intravenous fluids (3,000 c.c. of 5 per cent glucose in normal saline daily) and small doses of insulin. She responded well; acetone disappeared from the urine and the vomiting stopped. At this time the patient was started on 10 milligrams of vitamin B₁ and 50 milligrams of nicotinic acid daily.

Thirty-six hours after admission, the patient's pulse suddenly rose from 80 to 150 per minute and remained at that level. When the heart was examined, the point of maximal impulse was found to be in the fifth interspace, 0.5 centimeter outside the midclavicular line. The rhythm was regular, but the sounds of poor quality. The patient began to experience severe dyspnea; respirations increased from 22 to 40 per minute and were shallow in character. There were occasional medium moist râles at the bases of both lungs. No edema was present. The blood pressure had dropped slightly, from 120/80 to 102/78. The urine contained one-plus albumin, 4.5 per cent sugar and three-plus acetone. The carbon dioxide combining power was 24.9 volumes per cent. The blood sugar was within normal limits; blood chlorides were 460 milligrams per hundred cubic centimeters. The patient reacted well to the previous treatment of 5 per cent glucose in saline, intravenously, and small doses of insulin.

In spite of the amelioration of the signs of ketosis, the patient's pulse and respirations persisted at their very rapid rate. On the second and third days after the onset of the episode of respiratory and circulatory failure, the patient developed edema involving the face, lower extremities and back. At the same time, a marked disproportion between fluid intake and output was noticed. In the forty-eight-hour period preceding the appearance of the edema, the patient received 7,000 c.c. of fluid and excreted 1,100 c.c. The specific gravity of the urine ranged between 1.020 and 1.028. Blood chemistry, except for a slight elevation in uric acid (6.5 milligrams), remained normal.

At this time the patient presented evidence of clouding of consciousness and disorientation as to time and place. She became mentally confused and her speech was less clear. The tachycardia was more pronounced, the ventricular rate surpassing 150 per minute. Numbness of the feet developed. The cranial nerves were intact, and there was no nystagmus. The superficial and deep reflexes were equal and apparently undiminished.

The electrocardiogram gave witness to myocardial damage. There was marked sinus tachycardia (140 beats per minute). The PR interval was .18 and the QRS .08. T_2 and T_3 were inverted, and there was a deep Q_3 . Attempts to lower the pulse rate with digitalis were ineffective.

The fourth day after the beginning of the circulatory and respiratory crisis, the patient's blood pressure dropped to 70/30 and the fetal heart was no longer heard. In view of the progressive circulatory and respiratory failure, it was deemed advisable to remove the fetus. After two unsuccessful Watson inductions, the membranes were ruptured. When the patient had been in labor for five hours and the head had rested on the perineum for forty minutes with no progress, a slightly macerated stillborn infant (dead twenty-four hours), weighing six pounds, was delivered by low Elliott forceps; this was five days after the sudden onset of circulatory and respiratory distress.

For the first fifty hours after delivery, the patient's condition remained critical. The respirations were 35 to 40 per minute, the ventricular rate 130 to 140 per minute, and the blood pressure 80/60. Twelve hours after delivery the temperature rose to 102° F., but returned to normal in twenty-four hours.

On the third day post partum the patient improved noticeably. At this time she was receiving 40 milligrams of vitamin B₁ a day and nicotinic acid to the amount of 100 milligrams daily, the smaller initial doses having been increased immediately following delivery. The pulse and respiratory rates and the blood pressure returned to normal levels. Marked diuresis, with a urine of low specific gravity, was noted. By this time neurologic examination furnished evidence of severe polyneuritis. The eyegrounds showed pale retinas; the disc margins, however, were distinct. Corneal and pharyngeal reflexes were absent, as were the biceps, triceps and abdominal reflexes. Knee and ankle jerks could not be elicited. No response was obtained to stimulation of the soles of the feet. There was marked weakness of the extremities, most pronounced in the distal portions. The lower extremities were definitely atrophied. The patient could not raise her legs from the bed, nor could she sit up alone. She gave variable and inconstant responses to cotton and pinprick. There appeared to be unmistakable hypesthesia and hypo-algesia in the arms and legs, more marked distally. Deep muscle and tendon pain was increased.

No evidence of myocardial damage was found electrocardiographically nine days after delivery. PR was .18, QRS was .08, T's in all leads were upright, and the deep Q_3 had disappeared.

During the patient's entire hospital stay, from October 10 to December 10, 1940, vitamin B complex was administered to replenish the loss resulting from persistent vomiting. In view of the pronounced manifestations of polyneuritis, however, huge doses of thiamin chloride, nicotinic acid and brewer's yeast were pushed, with gradual, but progressive, improvement.

In January, 1941, three months post partum, the patient still exhibited some weakness of the legs, particularly of the extensor muscles of the thighs. The marked wasting which was present on her discharge from the hospital was no longer evident. She walked with only slight difficulty. The biceps and triceps reflexes had returned, but the knee and ankle jerks were still absent. All dysesthesias of the arms and legs had disappeared. There was no abnormality of the cardiovascular system.

At the present writing, seven months post partum, practically normal muscular function has returned and the patient is able to walk well. The knee and ankle jerks can again be elicited. Recovery from a disease in which all three manifestations of vitamin B₁ deficiency were observed can now be said to be complete.

Discussion

Many divergent suggestions have been offered to explain the etiology of neuronitis of pregnancy. In 1854 Churchill¹ advanced anemia, uremia, rheumatism and hysteria as possible causes of the paralysis. Jaccoud² in 1864 gave the highly theoretical explanation that the paralysis is due to exhaustion of the nervous system by prolonged and continued excitement of the cord, whose impulses are transmitted by the uterine nerves, thus exhausting the excitability of that particular segment of the cord and closing the avenues by which motor impulses pass. A little later Jolly³ ascribed the paralysis to hysteria. Möbius⁴ in 1887 was one of the first to suggest a theory of autointoxication; he believed some "morbid condition" of the blood of the pregnant woman to be the causative factor. Tuilant,⁵ noticing that severe vomiting precedes the neuritis, suggested that lack of nourishment is the principal cause. Polyneuritis resulting from starvation has been reported by Sehlesinger⁶ and others, but histopathologic studies have been largely neglected. The reader is referred also to the papers of Whitfield⁷ and other writers.⁸⁻¹⁰

Polyneuritis of pregnancy (gestational neuronitis), alcoholic polyneuritis, diabetic, biliary and gastrogenous polyneuritides, postinfectious polyneuritis, Korsakow's syndrome and other similarly misleading names have concealed the true diagnosis of vitamin B₁ deficiency clinically and pathologically identical with the Oriental disease. These polyneuritides differ only in the particular mechanism by which the deficiency is brought about. Cowgill¹¹ has shown that the vitamin B₁ requirement of man is directly proportional to body weight, caloric intake and metabolism.

In pregnancy, the nausea that is so often experienced restricts the patient's diet to concentrated carbohydrates low in vitamin B₁ content. Then, because of vomiting, she fails to retain all that she ingests. Furthermore, her metabolic rate, and with it her vitamin B requirement, are elevated by gestation; it is possible also that the processes of assimilation are reduced. If the vomiting becomes persistent, modern scientific therapy of so-called "pernicious vomiting" tends to increase the severity of the avitaminosis. With forced fluids, a temporary relief of the anorexia and anhydremia may result, but the removal of the vitamins by the consequent diuresis may be actually detrimental in that the vitamin B complex is washed from an already depleted body.

The clinical and pathologic manifestations of vitamin B₁ deficiency in pregnancy are the same as those resulting from some of the causes

mentioned above. The disease may make its appearance in either one or a mixture of three recognized types:

1. The "neuritic" form, also known as "dry" beriberi, which involves the nervous system primarily.
2. The "wet" form, or "edematous" variety, which presents the clinical picture of diffuse edema, dependent and nondependent.
3. The "cardiac" type, which manifests itself by disturbances of the cardiovascular system.

The neurologic findings may be confined to the peripheral nerves or may reflect involvement of the spinal cord. Optic neuritis has also been reported. Korsakow,¹² who is credited with calling the attention of the medical profession to certain mental changes accompanying the polyneuritis of alcoholism, reported with Serbski similar mental changes in polyneuritis of pregnancy.

Anatomic examination of cases of gestational neuronitis brought to autopsy has revealed definite degenerative changes in the peripheral nerves. In the cases reported by Dustin,¹³ Lindemann¹⁴ and Job,¹⁵ degenerative changes were found also in the anterior horn cells of the spinal cord. These changes were most marked in the lumbar region and consisted of loss of Nissl substance, swellings of the cells, eccentricity of the nuclei and occasional cell necrosis. Similar changes were demonstrated in the bodies examined post mortem by Berkwitz and Lufkin.¹⁶ Petechial hemorrhages of the brain and spinal cord were also observed; these, however, are not to be considered characteristic, as such changes are often observed in cases of severe dehydration. Cline,¹⁷ Mills¹⁸ and Patten¹⁹ have also reported on multiple neuritis of pregnancy.

As a result of recent observations and investigations, the relation of vitamin B₁ deficiency to heart disease has become firmly established. Aalsmeer and Wennebach,²⁰ in their studies of beriberi in Java, repeatedly noticed the occurrence of heart failure in the disease. On post-mortem examination of many of their cases, they recorded edema and "hydropic degeneration" of the myocardium. In 1933, Hauns and Warter²¹ described four cases of myocardial disease associated with polyneuritis. In the same year, Campbell and Allison²² reported in Ireland a series of eight cases of polyneuritis in which the symptoms of cardiovascular dysfunction were more prominent than the neuritic signs; they explained the cardiac disturbances on an infective basis. The relationship to nutritional deficiency, however, is too obvious to be ignored. Scott and Herrmann²³ cited cardiac manifestations of beriberi among the rice workers of Louisiana. Riesman and Davidson²⁴ described a case of beriberi heart following severe voluntary dietary restrictions. In 1936, Weiss and Wilkins,²⁵ in reporting cases of "wet" beriberi with cardiovascular disturbances, stressed the relationship of the disease to vitamin B₁ deficiency; the administration of vitamin B was followed by marked improvement. Furthermore, Weiss and his co-workers^{26, 27} have reproduced cardiac disorders in animals fed a thiamin-deficient diet; these disturbances disappeared after the administration of thiamin chloride.

Jones and Sure²⁸ reported on a group of eighteen cases of cardiac insufficiency treated successfully with high vitamin B₁ concentrate. In the case of severe heart failure described by Hashimoto²⁹ in 1937, the intravenous administration of thiamin chloride brought rapid relief

from precordial distress, dyspnea and nausea. In 1938, Nylin³⁰ published his observations on cases of beriberi heart with severe failure; these showed prompt improvement following the administration of thiamin chloride. Yudkin³¹ in 1938 presented a case of beriberi with cardiac manifestations which responded to thiamin chloride therapy.

Dustin, Weyler and Roberts³² analyzed the electrocardiographic changes in cases in which there were histories of unbalanced diet and clinical evidence of vitamin B₁ deficiency. They noticed a rapid rate, increase in duration of the electric systole, tendency to low voltage, and flattening of the T waves in leads I, II and III. Defects in the electrocardiogram disappeared following treatment with thiamin chloride. Williams, Mason and Smith³³ demonstrated similar changes in the electrocardiograms of four young women who had followed diets deficient in vitamin B₁. Weiss, Haynes and Zoll²⁷ observed like electrocardiographic changes in vitamin B-deficient rats, where also disappearance of the defects followed dosage with vitamin B₁.

In the case reported here, all three manifestations of vitamin B₁ deficiency appeared, all secondary to prolonged, persistent vomiting in the last trimester of pregnancy. On the patient's admission to the hospital, mild signs of peripheral neuritis were observed. She was therefore given what was considered to be an ample amount of vitamin B in all forms. However, in view of the more serious complications of vitamin B₁ deficiency that subsequently developed, it would appear that the initial dosage was insufficient. In addition, it must be remembered that this patient was treated primarily for her "pernicious vomiting" with large amounts of intravenous fluids, which, by the consequent diuresis, probably further reduced her already depleted vitamin B stores.

The sudden increase in pulse rate together with the change in quality of the heart sounds, the fall in blood pressure and the grossly detectable enlargement of the heart associated with the changes in the electrocardiogram, reflect the damage sustained by the cardiovascular system as a result of vitamin B₁ deficiency. The suddenness with which cardiac failure can occur during the course of the disease has been described in several of the articles cited previously.²⁵⁻²⁷

The appearance of edema in the second and third days after the onset of circulatory failure, and the associated oliguria with highly concentrated urine, can categorically be described as the "wet" type of beriberi.

The marked increase in efficiency of the circulation, namely, the disappearance of the signs and symptoms of vasomotor collapse, the improvement in quality of the heart sounds and the disappearance of all defects in the electrocardiogram, in contrast to the lag in improvement of the neurologic disorders following intensive vitamin B therapy furnishes definite evidence of myocardial damage.

The diuresis which took place during the period of improvement, both of which succeeded the increase in dosage of vitamin B, is to be noted. A similar observation has been made by Jones and Bramwell.³⁴

The lack of parallelism between the rates of improvement in circulatory and nervous function is striking. Apparently the cardiac disturbances respond quickly and completely to intensive vitamin B therapy. In Hashimoto's²⁹ case, the clinical manifestations of both right and left ventricular failure improved dramatically after the in-

travenous administration of vitamin B₁ (thiamin chloride). Van Bogacrt³⁵ in 1938 described the case of a young man who had developed cardiac failure as a result of alcoholic beriberi; the patient recovered rapidly when treated with thiamin chloride. In the experiments performed by Weiss and his associates,²⁵⁻²⁷ in which cardiac disturbances were induced in animals fed a thiamin-deficient diet, the disappearance of symptoms following the administration of thiamin chloride was prompt and rapid. Similar experiments were done by de Soldati,³⁶ who in addition demonstrated the swiftness with which defects in the electrocardiogram are remedied by the use of thiamin chloride in deficiency animals (dogs). Feil³⁷ and Keefer³⁸ also gave their attention to this problem.

The neuritic manifestations in the case reported herewith responded very slowly to vitamin B₁ therapy. The long interval that elapsed before practically normal function was restored is perhaps indicative of more extensive changes than those involving the peripheral nerves. It would not be assuming too much to state that some damage was sustained by the gray matter of the anterior horns, particularly in the lumbar region.

Summary

A case is reported in which all three manifestations of vitamin B₁ deficiency were observed, namely, the "neuritic," "cardiac" and "edematous" varieties, all secondary to prolonged, persistent vomiting in the last trimester of pregnancy. The dramatic response of the cardiac dysfunction to vitamin B₁ therapy, in contrast to the lagging improvement of the nervous disturbances, is to be noted. The literature on vitamin B deficiency is reviewed.

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THE EFFECT OF A SALT-POOR DIET ON THE LENGTH OF LABOR

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IN THE last decade there have appeared a number of reports in the literature stating that a salt-poor diet in the latter part of pregnancy results in a shorter labor and often in less severe labor pains. This observation was first noted by Hofstein and Petrequin in 1931, by Karpatti, and several years later by Reeb and Israel. Two series of cases were reported in the United States in 1940 by Wadlow and by Pomerance and Daiehman. All these workers agree on the effects of a salt-free diet in shortening labor.

In view of the apparent success of these investigators it was decided to place 50 patients on a rigidly controlled salt-poor diet and to use 50 others for control. Patients of the Salvation Army Home and Hospital in Grand Rapids, Michigan, were available for this study. Since the patients were institutionalized it was possible to supervise their diet. Separate food without salt was prepared for those on the salt-poor diet, and they ate at separate tables at which salt was not served. All patients on the salt-poor diet were volunteers. All cases studied were primipara. They came from similar environments and the same doctor gave prenatal care and delivered all patients in both groups in about the same period of time. The length of time for which patients were kept on a salt-poor diet ranged from four to nineteen weeks. In order to determine the extent of the salt-poor diet, chloride determinations were made weekly on 24-hour urine specimens.

Only the normal deliveries were used for the analysis of the results. All labors were of spontaneous onset. Most of the deliveries were by

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low forceps, only 15 per cent of the salt-poor group and 19 per cent of the control terminated spontaneously. Toxemias, of which there were five in the control and three in the salt-poor group, and breech extractions of which there were four in the control and two in the salt-poor group, were excluded.

The average weight gain in pregnancy is comparable in both groups. The control group gained 23.2 pounds, while the salt-poor group gained 21.4 pounds. The groups are also comparable with respect to age. The average age of the control is 18.2 while that of the salt-poor group is 19.2 years.

Sixty-five per cent of the control and 75 per cent of the salt-poor group were below 20 years of age. Since this comparability minimizes the effects of age on the duration of labor, it is interesting to note that the length of labor of the different age groups is quite constant in the salt-poor group and variable in the control. (Table I.)

TABLE I

AGE	SALT-POOR	LENGTH OF LABOR—HOURS	CONTROL	LENGTH OF LABOR—HOURS
	NO. CASES		NO. CASES	
14 to 16	7	8.1	9	8.5
17 to 19	25	7.7	22	10.7
20 to 22	10	7.5	7	9.0
23 to 25	4	7.5	3	4.9

It should be noted, however, that textbooks give the average duration of labor in primipara as 18 hours and in multipara as 12 hours. Adair, Dieckmann and co-workers in some 500 normal patients found the average duration to be 14.8 hours for primipara and 8.4 hours for multipara. Furthermore, Dieckmann and Brown found the average duration of labor in toxemic patients to be 16.3 hours for primipara and 9 hours for multipara. They did note that the labor in multiparous patients with edema was two hours less than those without edema. Many of the edematous patients had been on a salt-poor diet for days or even several weeks. It is obvious that the duration of normal labor in both primipara and multipara is decidedly less than the usual figures given in textbooks. Therefore, studies of the effect of a salt-poor diet must be compared with a control group, instead of data taken from textbooks.

The results and their statistical treatment are given in Table II.

TABLE II

	NO. CASES	MEAN HOURS	RANGE	ST. DEV.	ST. ERROR	SIGNIFICANCE RATIO
Salt-Poor	46	7.28	1-26	4.39	.65	1.50
Control	41	9.02	2-35	6.13	.96	

Although there is a difference of 1.74 hours in the length of labor between the control and the salt-poor group, the individual variations in the groups were such that this difference is not statistically sig-

nificant. Here again it may be noted from the differences in range and in standard deviation that the variations in the length of labor were much smaller in the salt-poor than in the control group.

For comparison the results from other papers on this subject are given in Table III. Only primiparous normal deliveries are included in the table.

TABLE III

AUTHOR	SALT-POOR		CONTROL	
	NO. CASES	LENGTH OF LABOR—HOURS	NO. CASES	LENGTH OF LABOR—HOURS
Hofstein & Petrequin	5	3.96*		
Reeb & Israel	10	4.03* (4.65)		
Reeb	56	5.25* (6.0)		
Pomerance & Daichman	51	9.9	33	22.9
Wadlow	34	6.58	100	13.08

*These figures indicate time of complete dilatation while figures in parentheses are calculated time of delivery.

The figure 22.9 hours for normal labor does not correspond with the usual observations and, of course, should not have been used for comparison with their treated group of patients. The differences in the length of labor between the control and the salt-poor groups shown in the above table are much greater than reported here. The length of labor of the salt-poor group agrees well with that given by Wadlow but the length of labor of the control group is much lower than either of the two reported in Table III. Wadlow does not state exactly how long his patients were restricted in salt intake, but the patients of Pomerance and Daichman were kept on a salt-poor diet for about six months. It is highly improbable that any of the patients maintained a salt-poor diet for six months, primarily because food is so unpalatable without salt, and secondly, because of the difficulties involved in obtaining such a diet. Seventy per cent of the patients reported in this paper were on a salt-poor diet for no longer than ten weeks. Unfortunately, the diet contained an excessive amount of salt.

If a salt-poor diet in the latter part of pregnancy shortens labor, the length of labor might show some variation with the duration of the salt-poor diet.

TABLE IV

NO. CASES	DURATION OF SALT-POOR DIET IN WEEKS	LENGTH OF LABOR—HOURS
18	3 to 6	8.0
13	7 to 10	7.2
11	11 to 14	7.2
2	15 to 18	7.0

There is a tendency for the length of labor to decrease with the duration of the salt-poor diet but it is not very marked. There is a noticeable reduction after the sixth week. From then on it does not seem to make much difference how much longer the salt is restricted.

Since all of the patients under consideration had normal pregnancies, we can consider the 24-hour chloride output as an indication of the efficacy of the salt-poor diet and may note how the length of labor varies with the extent of salt restriction.

TABLE V

	GRAMS SODIUM CHLORIDE		
	5 TO 5.9	6 TO 6.9	7 TO 7.9
No. Cases	6	14	7
Length of Labor—Hours	6.5	7.6	10.7

There seems to be a marked tendency for the duration of labor to increase with increasing salt output. Or to put it another way, the length of labor seems to decrease with greater salt restriction. The greater increase in the 7 to 7.9 group is due to one 26-hour labor without which the average length of labor for that group is 8.1 hours. A few scattered cases in other categories were not included in the table.

A salt-free diet implies that there is less than a gram of sodium chloride ingested per 24 hours. A salt-poor diet implies that the intake of sodium chloride is less than three grams per 24 hours. Dieckmann and Brown have stated that the pregnant patient with toxemia is, as a rule, adhering to her diet if the 24-hour excretion of sodium chloride in the urine is less than three grams. This, of course, would not hold in patients with an oliguria or with marked edema. It is disappointing to note that although all pregnancies studied were normal and the diets presumably strictly adhered to, yet the sodium chloride excretion on a salt-poor diet averaged about 6.5 grams per 24 hours. Unfortunately no studies could be made of the control group. I believe that the patients in my series were as carefully controlled as any reported in the literature with the possible exception of Reeb and Israel who did not consider a diet salt-free unless the 24-hour excretion of sodium chloride was less than two grams per liter. However, since the average 24-hour urine volume is 1,500 c.c. this would mean that the minimum excretion of sodium chloride by their patients was three grams per 24 hours, and the average excretion could have been and probably was much more.

There were fewer patients with toxemia in the salt-poor group than in the control which, of course, is to be expected.

Summary

1. A group of 50 patients were kept on a salt-poor diet for from 4 to 19 weeks before term, and their length of labor compared with that of another group of 50 used as a control.

2. These two groups were comparable with respect to age, environment, diets, and obstetric treatment.

3. The salt-poor group had a mean length labor 1.74 hours shorter than the control, but this difference was not found to be statistically significant.

4. There were smaller variations in the length of labor in the salt-poor diet group than in the control.

5. The tendency for labor to be shorter with greater salt restriction and with increasing duration of the salt-poor diet would seem to indicate that there might be a marked decrease in the length of labor with a true salt-poor diet.

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LEUCEMIA AND PREGNANCY

A Case Report and Review of the Literature

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A CASE of chronic myelogenous leucemia associated with pregnancy was recently encountered by us. The coexistence of pregnancy and leucemia is rare. A report of our case and a review of the literature are herewith presented.

Case Report

The patient, a 31-year-old white female, gravida viii, para vii, was referred to Kings County Hospital on December 19, 1942 by a local physician who had seen her earlier on the day of admission. She had had no prenatal care for this pregnancy. Her last menstrual period had begun on March 4, 1942; and the expected date of her confinement had been placed on December 11, 1942. Labor pains had begun at 2 A.M. on the morning of admission, being weak and ineffective, recurring every 15 to 30 minutes. A bloody show was noted at 10 A.M. On admission, the membranes were intact. Pains were recurring at 5- to 10-minute intervals, lasting 30 seconds, and of moderate intensity. The patient had not felt fetal activity for 36 hours prior to admission. She had noted no toxic symptoms throughout the gestation, except for a rash on her face which had become worse of late.

Past History.—A diagnosis of chronic myelogenous leucemia had been made 1½ years previously, and the patient had been admitted

to a city hospital near her on 9/6/41 for irradiation therapy to the spleen. Blood count on 10/2/41 was as follows: R.B.C. 3,800,000; Hemoglobin 80%; W.B.C. 176,000. The differential count revealed 15 polymorphonuclear leucocytes, 32 metamyelocytes, 30 myelocytes, and 23 myeloblasts. A total of 1,350 r. units was administered to the spleen. A blood count on 10/9/41 revealed a 90% hemoglobin and R.B.C. 4,760,000. The patient was last seen on 4/15/42, at which time the W.B.C. was 80,000. She was given 100 r. units to the spleen on that visit. Family history was noncontributory. Venereal history was denied. There were no previous operations. Menstrual: 14 by 28 by 3, cycle always regular. Obstetrical: 7 previous deliveries, there being 4 female infants, 3 male infants, each spontaneously at term. First delivery 1931. Last delivery 1940. Largest child weighed 8¼ pounds at birth.

Physical Examination.—The patient was an emaciated, white female, appearing chronically ill, but in no acute distress. Temperature 99° F., pulse 88, respirations 22. There was a maculopapular eruption on the face and chin, with some crusting present. The lungs were clear to percussion and auscultation. The heart sounds were of fair quality. No thrill or murmurs. Blood pressure 134/96. The spleen was palpable in the left upper quadrant, filled the entire left side of the abdomen, extended down almost to the iliac crest on the left, was solid, firm, not tender. The fundus of the uterus extended four fingers above the umbilicus. A fetal head was palpable in the fundus, while the breech was dipping in the pelvis. No fetal heart was heard. Pelvic measurements were ample. There was no lymphadenopathy. There was no edema of the extremities. On rectal examination, the cervix was not yet effaced or dilated.

Laboratory Data.—Urine was negative. R.B.C. 3,200,000. Hemoglobin 55%. W.B.C. 250,000. Differential count as follows: polymorphonuclear neutrophils 40, myeloblasts 10, metamyelocytes 25, myelocytes 15, lymphocytes 10.

At 4:20 P.M. on day of admission, patient delivered spontaneously a 6-pound stillborn male infant, LSA, frank breech presentation. Infant was macerated, but appeared normally developed in all respects. Duration of labor, 14½ hours. Blood loss minimal.

The temperature was septic in type subsequent to delivery, rising to 102.6° F. orally on the first post-partum day, and rising less each successive day thereafter. The patient offered no complaints. The lochia was always adequate in amount and was not foul. There was no abnormal tenderness of the fundus or pelvic organs. Fundus remained firm and was involuting normally. Breasts were soft and atrophic. Faeal lesions cleared up with balsam of peru and sulfur ointment. The patient was placed on a sulfathiazole routine empirically on 12/23/42. On 12/26/42, the patient complained of pain in her left ear. Examination revealed a left acute catarrhal otitis media, not marked, associated with a catarrhal rhinitis.

Throughout her hospital course, the patient refused many of her medications. She was uncooperative, depressed, and occasionally emotionally unstable. She refused blood transfusions. She refused food. On December 26, 1942, the patient signed her release and left the ward, despite advice to the contrary. The temperature on discharge was 99.6° F. orally, pulse 120.

The patient failed to return to us for any subsequent postpartum checkup; but when called upon by a member of the Visiting Nurses Association, the patient was found to be up and around, able to do her housework, and offering no complaints. She was advised to return to the city hospital nearest her, which had given her the irradiation therapy previously, for further blood studies and possible irradiation courses. The patient was last seen there on June 2, 1943, at which time her condition was fair, and she was given 600 r. units to the spleen.

Review of Literature

The coexistence of pregnancy and leucemia is rare. So far as is known, there have been only two men who have themselves seen as many as three cases of leucemia associated with pregnancy.⁵³ Grier and Riechter,⁸⁴ in 1939, reported a total of 75 cases collected from the literature, of which they used 62 cases for statistical studies. Extensive summaries of the literature have been previously reported by Kosmak,²⁹ Ohlsson,⁴¹ Bower and Clark,⁴² Neumann,⁴⁷ Debiassi,⁶⁰ Garassi,⁶⁵ Mehta,⁷² and Forkner.⁸⁰

At the present time, we have been able to collect references to 111 cases, of which in 79, we feel the diagnosis of leucemia associated with pregnancy is sufficiently well enough substantiated to be used for statistical purposes.

There doubtless have been a number of cases of pregnancy occurring with leucemia which have never been reported in the literature. Other cases have gone unnoticed, because they were included in surveys and topical discussions of leucemia, with no special emphasis placed on the presence of pregnancy.

As first noted by Forkner,⁸⁰ the cases reported by Ingle,² Stillman,⁶ and Sutcliffe²¹ cannot be accepted because the diagnoses were not definitely established and it is possible that the patients were not leucemic. In the cases reported by Paterson (3 cases),¹ Greene (2nd case),³ Herman,¹³ and Galabin,¹⁴ the data are incomplete and though these may have been cases of leucemia associated with pregnancy, they cannot be accepted as such. The case reports presented by Nagy,³⁸ Donati,⁷³ Tschopp,⁸⁵ and Laforet⁹⁴ could not be obtained for inclusion in our study. In the cases reported by Savaré (2 cases),¹⁸ Debiassi (1st case),⁶⁰ and Pontoni,⁷⁴ the data presented seemed to suggest diagnoses other than leucemia and hence are not included here. In 8 other cases, the authors, i.e., Brant;³⁵ Schreiner and Mattiek;³⁹ Sergeant and Mignot;⁴³ Hauch;⁸⁶ and Erf, Tuttle, and Lawrence⁵¹ have merely mentioned that they had encountered cases of pregnancy associated with leucemia. The data thus presented are inadequate for statistical use.

A few cases of leucemia beginning after the termination of pregnancy have been reported. The cases observed by Jaggard,⁷ Schenk,³⁶ Haining, Kimball, and Janes,⁶⁸ and by Forkner⁸⁰ are described elsewhere in more detail. Forkner cites the observations of Ward²⁵ who found 4 cases in which leucemia began soon after parturition. Forkner also includes the case report by Marmol who observed a fatal case of leucemia, beginning two months after a normal childbirth. Leube and Fleischner⁵ described a case of myelogenous leucemia developing 4

months post partum, which ended fatally six weeks later. The case reported by Isaacs⁷⁵ is unusual in that the patient who was suffering from lymphosarcoma had a remission during pregnancy, with the onset of a lymphosarcoma cell leucemia eight months post partum.

The association of pregnancy with leucemia etiologically, is a factor to be considered. Cameron⁵ favored the idea that a reciprocal relationship existed between the two. Sanger⁴ stated that pregnancy neither affected the origin nor the course of leucemia. Debiasi⁶⁰ felt that, though pregnancy was not the etiological factor in the production of leucemia, it at least acted as the releasing cause. Hussy⁶⁶ conjectured that leucemia was due to a toxic principle elaborated by the pregnancy.

In classifying our cases depending upon the blood studies, we found 34 acute leucemias associated with pregnancy as compared to 45 chronic cases. Statistics on 75 cases developing leucemia prior to or during pregnancy are herewith reported.

Of the acute cases, 17 were of the myelogenous type, 9 were lymphatic, 2 hemocytoblastic, and 3 were unclassified. The onset of the disease in all but two cases occurred after the onset of pregnancy. The disease seemed to bear no other relationship in onset to the length of gestation, except that several more cases were reported as beginning in the seventh month than for the other months of gestation. Parity likewise seemed to bear no relationship to the onset of the disease; and as would be expected, the greater number of cases was noted in primiparas and uniparas. The average age of the patient at the time of onset of the leucemia was 28.04 years. Life expectancy after onset of the disease averaged about ten weeks. Maternal mortality was 100 per cent. Four died during pregnancy; 5 died during parturition; 22 died post partum. Only two cases lived as long as 14 days after delivery. Fetal mortality was 60 per cent, there being 9 still-born infants and 3 neonatal deaths as compared to 8 live babies obtained. Severe post-partum hemorrhage was encountered in 5 cases, which was fatal in 2 instances. Of 20 cases which were not artificially interrupted, 9 proceeded to term, while 11 had spontaneous induction of premature labor. Only three stillborn infants were obtained when the pregnancy was allowed to proceed to term.

The prognosis seemed better if the patient was affected with the chronic type of leucemia. Of the 44 cases thus included here, 41 were of the myelogenous and 3 were of the lymphatic type. The average age of the patient at the time of onset of the disease in chronic leucemias was 30.63 years. Though observed in three primiparous patients, chronic leucemia seemed more closely associated with multiparity than did the acute forms. Only 6 cases developed chronic leucemia during the pregnancy, 51.3 per cent having had chronic leucemia for longer than 1 year before conception occurred. Maternal mortality here reached 36.5 per cent. One patient died undelivered, one during parturition, one shortly post partum, and 12 within one year after parturition. Of those cases not interrupted, 20 went on to full term before labor began. In 2 other instances, labor began spontaneously at 8½ months; in 8 cases, labor began spontaneously at 8 months or less. Severe hemorrhage was noted in only three cases, it being fatal in one of these three. Fetal mortality in the case of chronic leucemias was 16.4 per cent. Only two stillborn infants were noted: also three neonatal deaths due to prematurity. Healthy twins were delivered on two occasions.

As noted previously, pregnancy complicating chronic lymphatic leucemia is very infrequent. Russell⁶³ considered his case as being an example of the lymphogenous type and as such, is included here; although Grier and Richter felt that it should be included as an acute or subacute type because of the rapid course of the disease after onset. Langer,⁶⁹ in 1935, reported a case of chronic lymphatic leucemia, present for 3 years, complicated by pregnancy. A normal infant was delivered at term without ill effect to the mother. Harrison and Reeves,⁸⁹ in 1939, reported a case of chronic lymphatic leucemia of 8 months duration complicated by pregnancy, on whom an abortion was induced at 2 to 3 months gestation, without ill effect to the mother.

Jaggard,⁷ in 1890, described the first case of leucemia developing in the post-partum period. His patient, a 34-year-old multipara, after an apparently normal gestation and parturition, developed an acute leucemia 6 weeks later. Schenk,³⁶ in 1923, reported the case of a 21-year-old female who had a spontaneous abortion at 2 months' gestation. Three months later she was operated for what proved to be a ruptured corpus luteum cyst, immediately after which she developed an acute myelogenous leucemia. The case reported by Haining, Kimball, and Janes⁶⁸ was unusual, in that the patient developed an acute monocytic leucemia approximately 6 months after a normal delivery. The patient died 6 months later, following a left inguinal colostomy for intestinal obstruction due to a localized reticulosis of the rectum. Forkner⁸⁰ reported the onset of a subacute or chronic myelogenous leucemia, beginning late in the pregnancy or early in the puerperium, the patient dying ten months after parturition and the onset of symptoms.

Leucemia seems to predispose to spontaneous induction of premature labor. Of 49 cases of acute and chronic leucemias allowed to progress in their pregnancies without interference, 21 cases, or 42.8 per cent, developed premature labor.

Likewise, cases which had been subjected to considerable irradiation by either roentgen ray or radium and in whom sterilization might well be considered a good possibility by virtue of this exposure, have conceived and carried to term, delivering normal infants.^{28, 33, 42, 44, 45, 81}

Although hemorrhagic diatheses are supposedly part of the leucemic picture, it is to be noted that only three fatal hemorrhages were observed in a series of 75 cases. The case of Lazarus and Fleischmann¹⁵ died of hemorrhage in the third stage of labor, following a spontaneous abortion at 5 months' gestation. The case of Geller⁴⁹ had a fatal hemorrhage 2 hours after a cesarean section. Saidl⁵³ ascribed the fatality in his case to post-partum hemorrhage due to uterine atony.

Several authors have observed that their patients withstood parturition fairly well, only to go into profound collapse shortly thereafter, from which they failed to respond despite vigorous and often heroic treatment. Exitus was usually rapid following the collapse. No explanation for this was determined at necropsy.

An acute exacerbation of the leucemic process has been frequently noted following parturition. The white cell count shows a rapid elevation of immature cells which can only be controlled by appropriate measures, preferably irradiation. For the most part, however, it would seem that the course of leucemia is not greatly, if at all, affected by the pregnancy. In a few instances, overdistention of the abdomen as a result of the enlarging uterus in the presence of a greatly enlarged liver and spleen has caused discomfort to the patient. Herman¹³ felt

that under such circumstances, premature termination of the pregnancy would be advisable.

Autopsies on leucemic females have frequently shown extensive leucemic infiltrations of the genital tract, especially of the ovaries and uterus. This would seem to limit the frequency of pregnancies occurring with the disease, but as reported by Cameron⁵ and Neumann,⁴⁷ several pregnancies may be observed in the same patient during the course of her disease.

Hofstein⁵⁵ favors the theory that the prognosis for the mother decreases with each successive pregnancy; and that in the late stages of leucemia, pregnancy is not well supported. If pregnancy occurs during the first year or two of chronic leucemia, Hofstein feels that there is a good chance of delivery at term without much danger for the mother. Neumann⁴⁷ and Brandstrup⁷⁶ also adhere to these views.

No leucemic child has ever been delivered of a leucemic mother. This is hardly what one would expect. Leucemia has been transmitted from one animal to another in the laboratory, using related mice or fowl. It is therefore indeed surprising that leucemia in the pregnant woman is not transmitted to the offspring, inasmuch as leucemic cells, much like neoplastic cells, seem able to invade surrounding and distant tissues.

Cameron⁵ observed a leucemic blood picture on the maternal side of the placenta in the intervillous spaces, with a normal blood picture on the fetal side in the chorionic villi. Lindbrones,²⁶ Hilbert,¹⁰ and Askanazy¹¹ made similar observations. It would seem that the placenta acts as a barrier to the transmission of the disease process.

Congenital leucemia has been observed, but in no case was the leucemic child ever born of leucemic parents. Sanger⁴ reported a case of a premature stillborn infant who at autopsy showed all the characteristics of a true leucemia. Koch³² reported a similar case in 1922. Geshichter and Widenhorn⁶⁷ in 1934 reported a case in which the infant died of acute leucemia 9½ hours after birth. In 1939, Morrison, Samwick, and Rubinstein⁸⁷ tabulated 27 cases which had been reported as being examples of congenital leucemia. Of these, the authors accepted 7 as being cases in which the diagnoses were truly substantiated.

Opinions concerning therapeutic procedures to be adopted in pregnant leucemic patients are by no means uniform. Ohlsson,⁴¹ Saidl,⁵³ Naujoks,⁵⁴ and Hofstein⁵⁵ advised that early pregnancy should be interrupted at once. In general, however, it is the opinion of most authors that the shock of interruption is just as great as at parturition. Inasmuch as the course or outcome are little if any affected by the progress of the pregnancy, it would seem advisable to allow the pregnancy to continue. Taussig⁷⁰ states that in acute leucemia there is so little to gain by the abortion that it hardly if ever is justified. Interruption may be justified in terminal cases where the possibility of saving a viable infant presents itself.

The use of arsenic as a method of treatment of chronic leucemia during the progress of pregnancy deserves consideration, and it may be shown that this is the most rational procedure. The undesirable effects on the fetus of irradiation, as pointed out by Rolleston,⁵¹ Murphy,⁹⁰ and Murphy, Shirlock, and Doll⁹² preclude its use during pregnancy. There is no contraindication to the use of Fowler's solution during pregnancy, and experimental evidence seems to indicate that inorganic arsenic reacts favorably on the health and physical state of the fetus.

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55 EIGHTH AVENUE
451 CLARKSON AVENUE

Sheehan, H. L., and McLetchie, H. G. B.: *Simmonds' Disease Due to Post-Partum Necrosis of the Anterior Pituitary*, *J. Obst. & Gynaec. Brit. Emp.* 50: 27, 1943.

The authors report a rather rare case of Simmonds' disease due to postpartum necrosis of the pituitary gland. The patient died six days after delivery of the child. The characteristic clinical course of the disease was present, and the findings were confirmed by autopsy. A true "pituitary cachexia" was present clinically.

Treatment of these cases is not very successful. Other authors (Sheehan and Murdoch) have found that the production of a subsequent pregnancy leads to definite clinical improvement. Endocrine substitution therapy has given some promising results. The patient should also be on a salt diet and should never go a single day without an adequate food intake.

WILLIAM BERMAN.

ECTOPIC DECIDUA IN VERMIFORM APPENDIX

Showing (1) Acute Appendicitis and (2) Acute Periappendicitis

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ALTHOUGH its occurrence in the appendix is well known enough to receive mention in obstetric textbooks, ectopic decidua, to our knowledge, has not been reported in the American literature as an incidental finding in a surgical specimen showing either acute appendicitis or acute periappendicitis. By discovery in our cases of decidua in the inflamed appendix during routine examination, the pathologist was able to make—in addition to that of acute appendicitis, and periappendicitis—the diagnosis of pregnancy without clinical information concerning the condition of the patient.

Case 1.—Pathologic Description: The Laboratory of the E. J. Meyer Memorial Hospital, Buffalo, New York, received for routine examination an appendix and an isolated fibroid which had been removed by Dr. James O'Connor from a 35-year-old white woman on April 17, 1942, at the DeGraff Memorial Hospital, North Tonawanda, New York. No other clinical information accompanied the specimens.

Appendix.—Microscopically, it revealed acute diffuse phlegmonous appendicitis with focal lesions in mucosa, and fibrinopurulent periappendicitis. Of particular interest were certain findings in the subserosa. In this layer, scattered at different levels, were complexes of decidual cells (Fig. 1). Some of these were situated close to the outer muscle layer. Some surrounded blood vessels. Others lay just beneath serosa where in places they formed elevations of the surface. In certain complexes, decidual cells were separated by edema. There was also interstitial infiltration of neutrophils. Many decidual cells showed regressive changes. Spaced serial sections of the appendix disclosed no signs of endometriosis.

Microscopically, the tumor was a leiomyoma. Interestingly enough, there were changes commonly found in pregnancy: interstitial edema and swelling of cells with double nuclei and mitotic figures. In its outer portion, the leiomyoma showed acute inflammation with leucocytic infiltration and with fibrinopurulent exudate. There was no decidual reaction on the surface.

The pathologic diagnosis was acute appendicitis and periappendicitis; ectopic decidua in appendix (pregnancy); leiomyoma.

Clinical History.—The patient entered the hospital April 17, 1942, with the complaint of nausea of 12 hours' duration. Abdominal tenderness and muscle spasm, and leucocytosis were found on examination. The last menstrual period occurred October 10, 1941.

At operation, the uterus was noted to be the size of a 7 months' pregnancy. A lemon-sized, pedunculated, subserous fibroid that presented itself anterior to the right tube was excised. When the cecum was exposed, purulent fluid escaped. The appendix was acutely inflamed. It was not adherent to uterus or adnexa. Sulfanilamide powder was

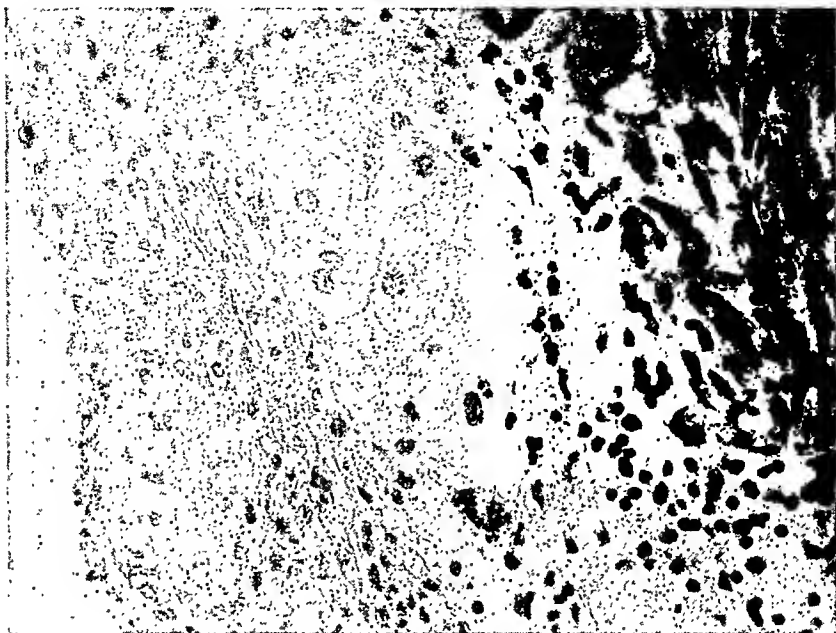


Fig. 1.—Decidual cells in acutely inflamed appendix of Case 1.

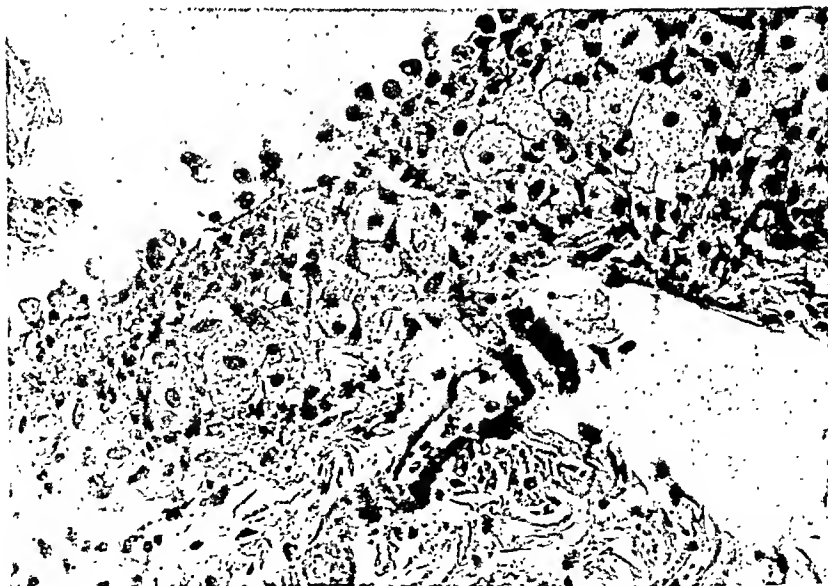


Fig. 2.—Decidual cells in appendix of Case 2.

placed in peritoneal cavity; drains were inserted. The postoperative diagnosis was acute appendicitis; localized peritonitis; uterine fibroid; pregnancy (about 7 months).

Except for cyanosis in the first three days after operation, the patient had an uneventful recovery. On June 28, 1942, she gave birth to a premature female infant, weight 4 pounds 4 ounces.

Case 2.—Pathologic Description: The Montgomery County Laboratory received an appendix with fibrinopurulent exudate both over and beneath its partially eroded serosa, which had been removed by Dr. Roman R. Vielyn from a 31-year-old white woman at St. Mary's Hospital, Amsterdam, New York.

Microscopic Findings.—The mucosa, submucosa and circular musculature of the appendix were intact. The longitudinal muscle showed slight neutrophilic infiltration in its outer portions, increasing rapidly in density until, in the subserosa, there appeared an intense and diffuse purulent infiltrate. The mesothelial cells were swollen and desquamated. Immediately beneath the mesothelium or a short distance within the subserosa and mesentery, were large cells arranged in small groups and concentric layers 2 to 6 cells in thickness. The cells measured from 15 to 30 micra in diameter, with sharp borders, having rounded forms at the edges of the groups and polygonal in the interior. The cytoplasm stained a pale, slightly bluish-pink, and in many cells, it contained a lacy structure of small vacuoles of varying size and shape, most marked at the periphery of the cell. The diffusely staining, rounded nuclei occupied about $\frac{1}{5}$ of the cell's diameter. A few cells contained 2 or 3 nuclei, but the majority were uninuclear.

The pathologic diagnosis was acute periappendicitis, ectopic decidua in appendix (pregnancy).

Clinical History.—The patient entered the hospital with the complaints of acute abdominal pain, nausea, vomiting, fever, and tenderness in the right lower quadrant. Appendectomy was performed ten hours after onset of symptoms. The temperature declined with descending oscillations until the patient's discharge from the hospital, 18 days after the operation.

The patient had one child, aged 7 years, and had had no other known pregnancies. The menstrual period before the abdominal episode was absent, but the date of the last period was not stated. During the three days following the operation there was vaginal bleeding stated by the patient to resemble a normal menstrual period. A Friedman test was negative on the twelfth postoperative day.

Summary

In two cases of acute appendicitis, and acute periappendicitis, decidual cells were observed in the subserosa of the surgically removed specimen. A diagnosis of pregnancy was made by the pathologist without clinical information. In the first case pregnancy was in the seventh month. In the second case sequence of events suggested that fetal death occurred in the first month.

EXTERNAL VERSION FOLLOWED BY PLACENTAL SEPARATION AND SHOCK: RECOVERY AFTER CESAREAN HYSTERECTOMY

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SINCE its introduction in 1807, external version (Wiegand method) has been used extensively to convert breech to more favorable cephalic presentations. In a collected review from 9 authors, Adair¹ reports only 2 patients with slight vaginal bleeding (presumably from placental separation) in 1,105 attempted external versions, and Newell² states that complications from external version are rare. Three additional cases^{4, 5} of premature separation of the placenta following external version have been collected. One maternal death occurred (Couvellaire uterus demonstrated at autopsy). The infants were stillborn.

Although external version favors a reduction of fetal mortality rate and is usually a safe and desirable procedure, optimistic reports concerning its safety^{1, 2} should not lead to the neglect of certain precautions. Such complications as compound presentation, premature rupture of the membranes with presentation of the cord, fetal death from cord entanglement, and premature separation of the normally implanted placenta should be avoided if possible. It is doubtful if external version is advisable in the presence of a hypertensive syndrome. The use of anesthesia to promote relaxation probably makes the procedure more hazardous. A recent patient at the University Hospitals illustrates these latter points.

Case No. 42-14109.—C. M., 33 years of age, para iii, gravida v, was admitted on December 12, 1942, approximately eight and one-half months pregnant. A history of a 33-pound weight gain and recent edema was obtained. Although hypertension had been discovered early in pregnancy, there were no subjective symptoms. The first pregnancy in 1929 was complicated by edema, proteinuria and hypertension, but succeeding pregnancies were not toxemic. The past medical history revealed: scarlet fever without sequelae, nonsurgical treatment for hyperthyroidism in 1929, and severe pyelitis of pregnancy in 1931. There was a maternal familial history of hypertensive disease.

Examination disclosed a blood pressure of 180/120 mm., one plus albuminuria, with a few granular casts, slight ankle edema, and a breech presentation of an 8½ months' gestation. Electrocardiogram, x-ray studies for cardiac size, kidney function tests, and blood chemistry were entirely normal. Ophthalmoscopic examination showed generalized arteriolar constriction, a condition compatible with permanent vascular damage. On two occasions the cold pressor test⁶ resulted in no significant rise in systolic blood pressure although the diastolic pressure rose 16 and 20 mm. A consulting ophthalmologist described retinal angiospasm while the hand was immersed in ice water. The response to barbiturates⁷ was a moderate decrease in systolic (30 mm.) without significant change in diastolic blood pressure.

During a hydration regimen⁸ no diuresis (weight loss), reduction of blood pressure, or decrease in proteinuria occurred. In fact, on Janu-

ary 2, 1943, the blood pressure reached 210/130 mm., and symptoms of headache, blurring of vision, and dizziness appeared. Induction of labor was considered advisable, and to obtain a cephalic presentation, a successful external version (Wiegand method) was performed on January 4, 1943. However, the infant returned spontaneously to a breech, and the second attempt at external version was unsuccessful.

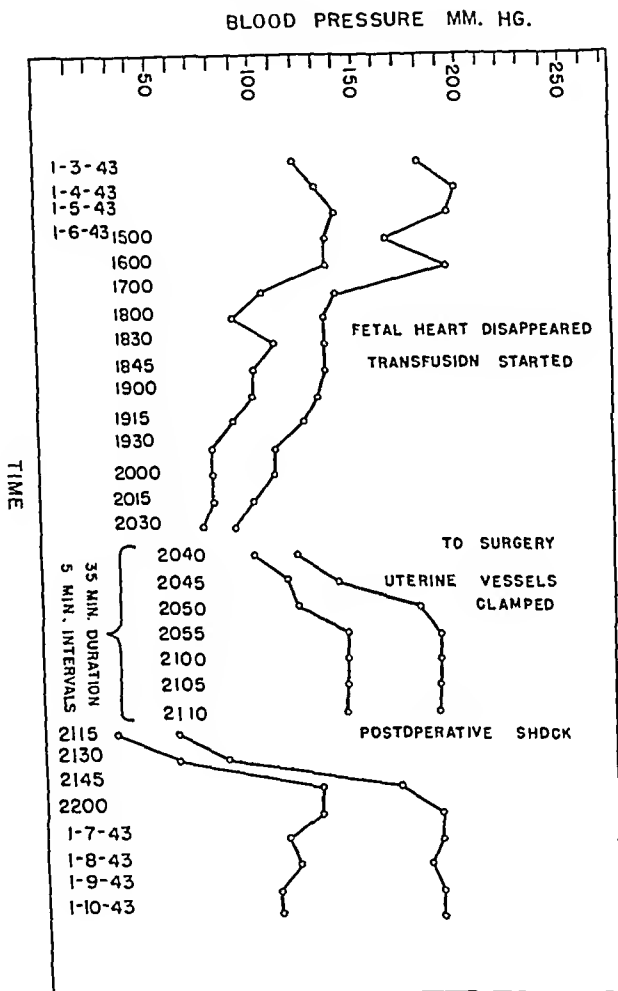


Fig. 1.—Blood pressure record showing abrupt rise when subtotal hysterectomy was performed. Inasmuch as the blood loss was minimal it is believed that some toxic substance (liberated from the placental site) accounted for the first episode of shock. It is believed that the second episode of shock resulted from the operative procedure. The hours in this graph designate Army-Navy time, — e.g., 1900 is 7 P. M.

Under cyclopropane anesthesia, a third external version was unsuccessful. A bipolar attempt (one finger in cervix to dislodge breech) at version also failed. The patient was transferred to bed, with a blood pressure of 195/140 mm. and normal fetal heart tones. Routine pituitrin induction of labor was started at 3 P.M. and the membranes ruptured spontaneously at 3:45. At 4 o'clock, weak contractions began and 150 c.c. of dark blood was passed vaginally. Following this bleeding episode the fetal heart tones disappeared and the blood pressure gradually declined (Fig. 1).

The importance of a steadily declining blood pressure without clinical improvement⁹ was appreciated. Therefore, blood transfusion was started at 6 P.M., and 1,500 c.c. of glucose citrate blood were given in the next few hours. Notwithstanding this supportive measure, the blood pressure continued to fall (100/80 mm., pulse 128/minute, at 7:45 P.M.) (Fig. 1). Cold, clammy skin and vomiting appeared to complete the clinical picture of shock. Examination disclosed an undilated cervix and no uterine contractions. An emergency subtotal hysterectomy was performed under cyclopropane anesthesia. As the uterine vessels were clamped, the blood pressure suddenly rose to a sustained high of 190/145 mm. Although the blood pressure fell to shock level soon after operation, normal readings were re-established within 15 minutes. An uncomplicated puerperium ensued. Kidney function studies and blood chemistry were entirely normal on the seventh postoperative day. The patient was discharged on the twelfth postoperative day with a blood pressure of 180/120 and no proteinuria.

TABLE I.—RESULTS OF COLD PRESSURE TEST*

PA-TIENT	HOS-PITAL NUMBER	P	G	RETINAL FINDINGS BEFORE COLD PRESSURE TEST			B.P. AT REST IN MM.	IMMERSION IN ICE WATER FOR 1 MINUTE		ANGIO-SPASM OBSERVED DURING ICE WATER IMMERSION
				GENER-ALIZED CON-STRICTION	LOCAL-IZED SPASM	NOR-MAL FUNDI		RISE IN SYSTOLIC B.P. MM.	RISE IN DIASTOLIC B.P. MM.	
E. M.	42-14090	9	10	+			150/90	30	24	+
E. C.	42-14039	5	6	+			160/100	10	20	+
W. H.	42-13620	0	1	+			180/120	20	24	+
A. F.	42-13626	0	1		+		150/110	10	20	+
C. M.	42-14109	3	5	+	+		176/110	14	16	+
M. D.	41-13248	0	1			+	150/90	26	30	+
M. P.	38-16344	0	1	+			180/120	40	40	+
B. H.	41-15534	0	1			+	140/90	0	16	+
M. S.	42-4494	0	1			+	130/80	8	20	+
E. K.	41-14173	0	1		+		150/104	10	20	+
M. Mc.	38-23122	5	6			+	140/94	20	14	+
F. S.	41-8121	0	1			+	130/84	34	24	+
M. S.	42-449	0	1	+			170/110	40	30	+

*Note the consistent rise in diastolic blood pressure (over 14 mm.) in those hypertensive patients exhibiting retinal angiospasm during immersion of the hand in ice water. The behavior of the systolic blood pressure was inconclusive. According to Selinger¹⁰ the most consistent retinal findings in pregnant patients exhibiting a hypertensive syndrome are generalized arteriolar constriction or localized vascular spasm.

In the group of patients demonstrating retinal angiospasm during ice water immersion, the clinical impression was: Moderately severe pre-eclampsia (A. F.), severe pre-eclampsia (M.D., M.S., E.K., F.S., M.S.), mild cardiovascular disease (E.C., B.H., M.M.) and severe cardiovascular disease (A.M., D.H., C.M., M.P.).

Examination of the gross specimen disclosed a few subserosal ecchymoses. Upon opening the uterus, a 2,600 gram, female infant was removed. The placenta which was attached to the anterosuperior portion of the body was three-quarters separated by a 200 c.c. retroplacental hematoma. Several sections through the uterus failed to show hemorrhagic infiltration.

Comment

In a patient with a hypertensive syndrome, external version under anesthesia is ill advised. It is difficult for the operator to refrain from vigorous manipulation when the abdominal musculature is relaxed.

The natural, muscular defenses of the conscious patient are good insurance against trauma during external version. In the case reviewed, bag induction of labor instead of attempted external version would probably have given more satisfactory results.

The progressive fall in blood pressure notwithstanding early blood transfusion, the appearance of clinical shock, and the rapid return to normal level when the uterine blood supply was interrupted, suggest a toxic substance (possibly released from the uterine placental site) as an etiologic factor. Although hemorrhage has been suggested as the principal cause of shock (and death) in patients with premature separation of the normally implanted placenta, blood loss in this case did not exceed 400 c.c., ordinarily an insignificant amount. It is difficult to explain the succession of events on any basis other than the liberation of a toxic substance from the uterus or placenta.

In pregnant patients with hypertension, the cold pressor test⁶ and response of the blood pressure to barbiturates⁷ have been suggested as aids in distinguishing between pre-eclampsia and hypertensive vascular disease. These tests have been successfully employed in selected cases. Recently, simultaneous ophthalmoscopic examination and cold pressor test have revealed angiospasm of retinal vessels. (See Table I.) In those patients exhibiting retinal angiospasm during the cold pressor test, a rise in diastolic blood pressure was a constant finding. The behavior of the systolic blood pressure in such cases is unreliable and probably unimportant. In a previous report⁷ renal suppression was obtained in hypertensive pregnant patients after prolonged immersion of the hand in ice water. It has been suggested that eclampsia, oliguria, anuria, and premature separation of the placenta complicating some hypertensions of pregnancy are due to angiospasm. Ophthalmoscopic examination and more attention to the response of the diastolic blood pressure may clarify the controversy regarding the diagnostic value of the cold pressor test.

Summary

1. External version in the presence of hypertension is not an entirely safe clinical procedure.
2. External version under anesthesia is dangerous.
3. The behavior of the blood pressure in the case reported suggests some liberated toxin as an etiologic factor in shock.
4. Evidence is advanced that angiospasm can be demonstrated in the fundi of hypertensive pregnant patients by use of the cold pressor test.

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PELVIC HEMATOMA COMPLICATING PARTURITION

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THE following is an unusual case of pelvic hematoma complicating parturition.

(Hosp. No. 415,058.)—On July 1, 1941, Mrs. K. F., a 27-year-old housewife, was admitted in labor on the obstetric service of The University Hospital.

The family and past histories were essentially negative. The antepartum examinations revealed no unusual findings.

At about 5 A.M., July 1, 1941, this para 0, gravida i, due June 22, 1941, began to have labor pains. When she entered the hospital at 9:15 A.M., she was having contractions every 3 to 4 minutes. The temperature, pulse rate, and respiration rate were 98.4°, 94, and 18 respectively. Physical examination revealed a well-developed, well-nourished, young, white woman at term in good health. The fetal heart, 140, was heard in the left lower quadrant. A slight amount of bloody, mucous show was visible. Rectal examination revealed the head at low station and the cervix to be 3½ fingers dilated. The total red count was 4.86 million; the hemoglobin was 16.4 Gm. (Sahli-Hellige method); the total white count was 12,400; and the differential white count was 74 per cent granulocytes and 26 per cent lymphocytes and monocytes. Urine examinations on entry and during the hospital stay were non-contributory.

By 11:20 A.M., the cervix was completely dilated. The membranes were ruptured artificially. At 11:34 A.M., a normal, living, female infant, weighing 4½ pounds, was delivered spontaneously with slight bleeding. One c.c. of pituitrin (obstetrical) was given. At 11:47 A.M., the placenta was expressed intact. One c.c. of ergotrate H, containing 1/320 grain, was given. A posterior vaginal wall first degree tear—¾ inch in length and just inside the mucocutaneous junction—was easily repaired with 20-day chromic catgut, size 0. At 12:15 P.M., the patient was returned to her room in good condition. Blood loss had been minimal.

At 6:30 P.M., the vulva was quite edematous. By 10 P.M., the patient had not voided; and was catheterized. At 1:15 A.M., ⅙ grain of morphine sulfate was given for restlessness. At 3 A.M., the patient was awake; and complained of pain in her abdomen. Although the uterus felt fairly firm, massaging resulted in a large amount of bright red blood flowing from the vagina and in the expulsion of a medium-sized clot. At 3:15 A.M., the pulse rate was becoming more rapid, having risen to 112 from 92 at 3 A.M. An ice bag was applied to the abdomen. By 4 A.M., the bleeding from the vagina had ceased; the uterus was firm; the pulse rate had fallen to 100; and the patient was asleep. At 5:30 A.M., the

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pulse rate was again rising; but the fundus was firm. At 6 A.M., the pulse, weak and thready, was continuing to become faster; and the patient, apprehensive and breathing rapidly and shallowly, became pale, cold, and clammy. External heat in the form of warm water bottles and blankets were applied. At about 6:30 A.M., the blood pressure was zero.

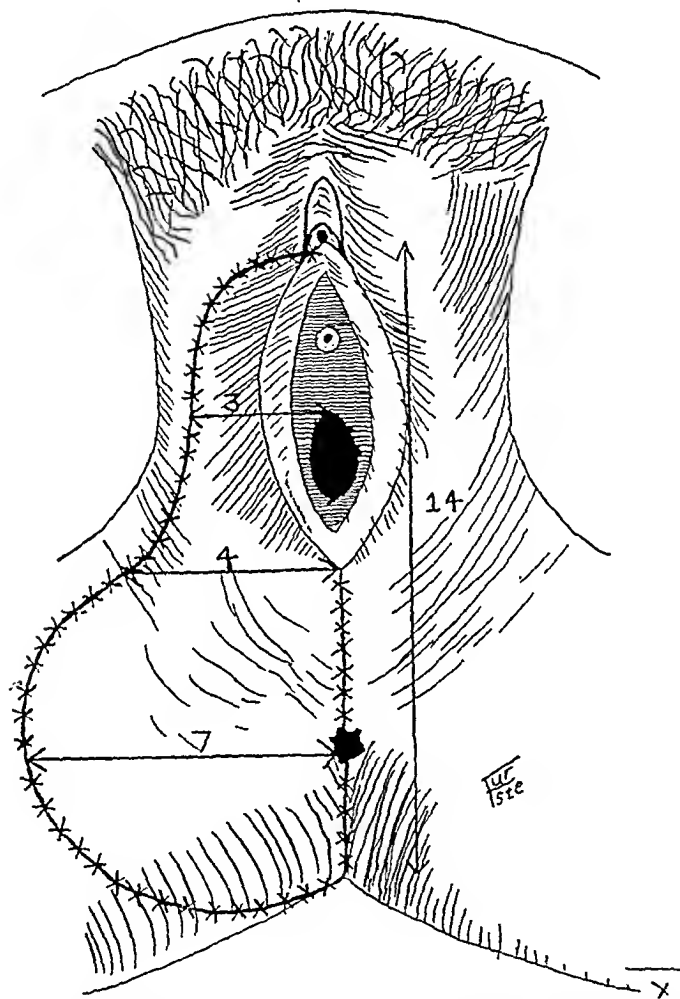


Fig. 1.—Extent of the visible portion of the hematoma. Numbers represent distances in cm. indicating the border of the visible portion of the hematoma.

Note that the hematomata were unilateral—being on the right side—and that the greatest visible extension was in the anal region where the outer border was 7 cm. from the anus.

The foot of the bed was elevated; more blankets and warm water bottles were placed over the extremities; and 1,000 c.c. of 10 per cent glucose in normal saline solution were administered intravenously. The pulse rate and blood pressure gradually decreased and increased respectively; the extremities became warmer; the amount of perspiring became less; and the breathing became slower, deeper, and easier.

After the shock was combated, the pulse rate fell from 100 at 8:30 A.M. to 72 at 10 P.M., and the blood pressure was steadily higher than 100/70. There became visible, however, large perineal hematomata.

From July 2 on, the post-partum period was uneventful, except for an elevation of the temperature to 102° and of the pulse rate to 110 on the fifth and sixth postdelivery days. On these two days, abdominal examination revealed a moderate, diffuse, right lower quadrant tenderness without muscle spasm; and rectal examination revealed, on the patient's right, a large mass of blood clots which measured at least 8 cm. in diameter, which extended up farther than the examining finger could reach, and which bulged markedly into the rectum and pushed it to the left. On the fourth of July, 9 grains of ferrous sulfate per day were started.

TABLE I. INCIDENCE OF PELVIC HEMATOMATA COMPLICATING PARTURITION
ACCORDING TO DIFFERENT AUTHORS

AUTHOR	INCIDENCE
Michaels and Herring ⁶	1 per 5,474
DeLee ¹	1 per 4,000
Moschkow ⁷	1 per 1,951
Williams ⁹	1 per 1,500
	or
	1 per 2,000
Dorland ¹⁵	1 per 1,600

TABLE II. PROGNOSIS IN CASES OF PELVIC HEMATOMATA COMPLICATING PARTURITION

SOURCE OF DATA	NO. OF CASES	NO. OF DEATHS	PER CENT OF DEATHS
Cases described by Hamilton ³	12	1	8
Cases of others found by Hamilton ³ in the literature	115	26	23
Michaels and Herring ^{6*}	8	2	25
Goodhand ^{2*}	1	0	0
Lamm and Lamm ^{4*}	1	0	0
Lipow ^{5*}	1	0	0
Furste and Koerper (this report)*	1	0	0
All reports	139	29	21

Hamilton³ found 144 cases of 18 other writers^{7, 9-13}; but, for these cases, he was able to obtain complete data on only 115 which are mentioned in this Table.

*These cases were not reviewed by Hamilton.³

On discharge from the hospital on July 16, the total red cell count was 3.24 million; the hemoglobin was 10 Gm. (Sahli-Hellige method); the red cells appeared to be normocytic and normochromic; the total white count was 22,700; and the differential white count was 86 per cent neutrophils, 2 per cent eosinophils, 11 per cent lymphocytes, and 1 per cent monocytes.

On July 23, the skin color, produced by the perineal hematoma, was only a faint blue. Vagino-rectal examination revealed, about 1/2 inch from the mucocutaneous junction on the right side of the posterior wall of the vagina, a somewhat tender, nonfluctuant mass, about 3 by 3 by 1 1/2 cm.; and did not reveal a mass in the broad ligament.

On June 10, 1942, the patient reported that, until about April, 1942, she had had slight pain on intercourse; but she had no other complaints. Vaginal examination revealed a slight cystocele, a uterus of normal size and shape and in an anterior position, and clear vaults without any palpable remainder of the hematoma. Likewise, rectal examination gave no indication of the previous hematoma.

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As emphasized by Koller, women who are particularly susceptible to thrombosis and embolism are those who are over 40 years old, have borne children, are obese, have varicosities, somatic and psychic exhaustion, have had previous thrombosis or embolism, have febrile disease or have undergone an operative delivery or operation, and those with myomas or malignant tumors or postoperative complications.

The causes of thrombosis are physical-chemical-biologic changes in the blood, changes in the blood circulation, damage to tissue and meteorologic influences.

Prophylaxis of thrombosis and embolism consists of careful preoperative preparation, position after operation, sufficient fluid intake, bed exercises, the use of blood coagulants, early rising, stimulation of the heart and circulation—before and after operation, proper nourishment and scrupulous operative technique.

In the Zurich clinic the incidence of thrombosis and embolism was 1 per cent after spontaneous labor and 2.6 per cent after vaginal operative delivery. Among the latter, the frequency was 4.2 per cent for forceps delivery, 5.2 per cent for manual removal of the placenta, and 7.2 per cent for cesarean section.

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SUBCUTANEOUS EMPHYSEMA COMPLICATING LABOR

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THE occurrence of subcutaneous emphysema during or after labor is a rare and somewhat alarming complication. Its rarity is attested to by the fact that few men have seen it more than once in a lifetime of practice, and the total number of reported cases is only 156.

Simmons in London reported the first case in 1784,^{1, 6} but the occurrence of the condition is alluded to even earlier. Louise Bourgeois⁶ midwife to the Queen of France published in her "Observations" in 1617, "I saw that she tried to stop crying out, and I implored her not to stop for fear that her throat would swell." De Paul,⁶ in 1842 first drew attention to the condition, reporting a death and autopsy. Haultecoeur⁴ in 1874 wrote the first thesis on the subject, collecting 13 cases. Since that time many new cases have appeared, Nicaisse¹ collected 54 in 1896, Kosmak⁷ 78 in 1904, Gordon⁶ 130 in 1927, Marony² 144 in 1933 and McCollum¹⁰ 151 in 1940. Since that time 5 more cases have been reported.

Report of a Case

The patient, Mrs. M. C., a 22-year-old white, para 0, gravida 1, was first seen in our clinic on September 28, 1942, 4 months pregnant. Her last menstrual period had begun on May 21, 1942, and lasted 5 days. The estimated date of confinement was February 28, 1943. Her previous history was entirely negative, except for urinary frequency of one year's duration.

Examination revealed a normal white female who was noted to be a hypothyroid type; her normal weight being about 180 pounds, and her height 63 inches. Measurements were adequate, intraspinous 27 cm., crests 28 cm., external conjugate 21½ cm., bi-ischial 8½ cm. The diagonal conjugate was not reached. The pelvis was of the gynecoid type and was felt to be ample. Blood pressure was 100/60 and the weight was 176. The height of the fundus was 17 cm. and the fetal heart was not heard. Wassermann report was negative, blood count was normal, showing red blood cells 4,240,000, white blood cells 7,250, hemoglobin 75 per cent (Tallquist). Polys 78, lymphs 22. Patient was put on calcium and ferrous sulfate. Pregnancy up to this time was uneventful except for slight nausea, vomiting, and frequency of urination.

The patient was next seen in clinic on November 9, 1942, at which time she had gained 9 pounds, blood pressure was 130/78, and she showed slight edema of the feet and hands. She was put on a restricted salt diet and told to return in two weeks. Patient was fairly well controlled during the remainder of her pregnancy, except for one small episode of elevated blood pressure (150/80) which responded to phenobarbital and rest. Patient was last seen in clinic on March 1, 1943, at which time the blood pressure was 120/60, weight 190, fundus measured 32 cm., position was ROA, and the fetal heart was heard in the right lower quadrant.

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Labor pains began at 2:00 A.M. March 2, 1943, and the patient was admitted to the hospital at 11:00 A.M. on this date. Examination revealed position ROA with the fetal heart audible in the right lower quadrant. On rectal examination the head was just above the spines, dilatation was one finger, and the cervix was thick. Pains were every 15 minutes and lasted for 30 seconds; contractions were not very severe. At 5:15 P.M. the membranes ruptured spontaneously and a heavy bloody show was noted. Examination at this time revealed dilatation to be three fingers, pains every 5 minutes lasting for 30 seconds, the head was just below the level of the spines and the position was ROA. Patient was given 3 gr. of seconal by rectum. At 6:25 P.M. patient was taken to the delivery room and at 7:00 P.M. delivered spontaneously of a living male infant. Right mediolateral episiotomy was done to facilitate delivery and this was repaired with subcutaneous 00 chromic catgut, with subcuticular closure of the skin. During the induction stage of the anesthetic (G. O. E.) the patient had a severe attack of vomiting, retching, and coughing; and gastric contents had to be aspirated by suction from the nose, mouth, and throat. After this the anesthesia proceeded smoothly.

Placenta was expressed intact and the blood loss was not excessive. The patient was returned to the ward in good condition. On reaction the patient complained of soreness in her throat and had a moderately severe cough. She was given codeine cough syrup 4 c.c. every 4 hours for this.

The first day after delivery it was noted that the patient's face was flushed and her respirations (24 per min.) were somewhat labored. Pulse was 96, temperature was 98.4° F. Râles were noted in the right posterior chest and there was slight suppression of the breath sounds. The next day x-ray revealed the presence of a bronchopneumonia of the right upper lobe, and an emphysema extending from the mediastinum up into the neck. The patient was complaining of difficulty in speaking and pain in the throat. Crepitus was noted in both supraclavicular areas and in the tissues of the upper chest wall, extending up to the angle of the jaw on both sides. Temperature was 101.2° F., pulse 128, respiration 30. The patient was flushed and perspiring freely, however, there was no cyanosis, and the patient did not appear to be overly distressed. Sulfathiazole was administered, Gm. II stat and Gm. I every 4 hours.

On March 5, temperature was 100.4° F., pulse 132, respiration 32, and the emphysema had spread up to the level of the ears on both sides. The neck pain and difficulty in speaking which she had experienced in the previous 2 days appeared much lessened. Patient's general condition was good and there was no evidence of cyanosis.

Sulfathiazole was discontinued on March 8 at which time temperature had been normal for 24 hours, pulse was 92, respirations 28. Blood sulfathiazole level was reported as 3.0 mg. per cent. Sputum examination showed no acid-fast organisms, but numerous gram-positive diplococci which did not type 1 to 33. Patient's general condition improved rapidly and the emphysema was completely gone, both clinically and by x-ray, on the 12th of March (tenth post-partum day). Patient was discharged from the hospital on March 17 at which time the chest was clear, the fundus well involuted and the perineum healed. When the patient was seen again in the clinic on April 9, 1943, the chest was clear and her general condition was excellent.

Summary

1. A case of subcutaneous emphysema associated with bronchopneumonia following labor and apparently resulting from severe retching and coughing during anesthesia is reported.

2. The emphysema in this case was probably due to rupture of overly distended pulmonary alveoli with leakage of air into the underlying pulmonic perivascular sheaths and passage by infiltration of the air along the sheaths to the mediastinum, from whence it followed the vessels of the trachea into the neck.

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PLACENTA ACCRETA

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CASE 1. In a Twin Pregnancy.—A young woman of 19, who was never curetted, never had any miscarriages nor operations of any kind, was being delivered by a midwife. Her first baby (boy) was delivered four hours before I was called in at the request of this midwife because she was unable to deliver the placenta. There was no hemorrhage. Upon external examination, a baby in the transverse position was diagnosed in utero. Fetal heart sounds were plainly heard.

The patient was immediately removed to the Flint-Goodridge Hospital where she was delivered of a second baby by an internal podalic version, in good condition. Attempts were made to deliver the placenta by expression, which failed; still there was no hemorrhage of any kind. After waiting for two hours the uterus was well contracted (an ampule of pitocin being given). Externally the fundus assumed a broad flattened shape instead of being rounded; traction on the cord showed no descent. Exploration under strict aseptic condition was done. There were two cords and two placentae adherent to the fundus with no line of demarcation whatever. No attempts were made to peel off the placentae. The patient was left alone until the next day: temperature 101.4° F. Ergotrate, grains 1/320 every four hours for four doses, was given. Infusion 1,500 c.c. 5 per cent glucose in saline were absorbed. The patient was typed for transfusion. Red cell count 3,750,000, white 10,600. Hb estimation 48 per cent. Urine negative.

Kahn, negative. After another attempt at trying to deliver the placenta had failed, the patient was prepared for hysterectomy. Since the status of the patient was that of a primarily infected case, a quick hysterectomy was done lasting 40 minutes, and 5 Gm. of sulfathiazole was placed in the cul-de-sac. Transfusion was given immediately, followed by two infusions of 1,000 c.c. 5 per cent glucose in saline two successive days following. The temperature rose to 102.6° F. the next day, then spiked for three successive days, following which it gradually subsided to normal after seven days. Patient was then discharged in three days in good condition.

Pathological Diagnosis: Double placenta accreta.

CASE 2. Associated With Rupture of the Uterus.—A well-nourished multipara was first treated 8/30/40 and was admitted for delivery, 9/6/40. She had had three normal deliveries prior to this. There was no hemorrhage nor retained placentas in her previous deliveries.

Blood pressure was 130/80, Wassermann negative. After approximately five hours of labor she was seized with sudden cramplike pains as though expulsion was imminent. She was placed on the delivery table for examination at which time the cervix was found to be dilated 2 cm. Within 10 minutes, there was profuse hemorrhage; the patient felt better but promptly went into shock. Coramine was administered and 1,000 c.c. 5 per cent glucose in saline as infusion was started; the patient seemed to rally and was removed to the operating room with a diagnosis of ruptured uterus. The presentation was vertex (O. R. A.). Fetal heart sounds were not audible and the mother was in poor condition from profuse hemorrhages which were continuing. She was immediately cross-matched. Laparotomy was performed. A high cesarean section was done; the baby (boy) was extracted and alive. Following this and in quick succession a supravaginal hysterectomy was accomplished but there was a rent in the right lateral aspect of the uterus at the site of the broad ligament and a large hematoma was enclosed in the ligament measuring approximately 3 by 3 inches in size and practically filling the right fornix. The patient still continued to bleed from this site. The ligament was opened, the hematoma removed and all bleeding points sutured with chromic catgut. The abdomen was closed in layers and 500 c.c. whole blood given. On the afternoon of the first day of operation the patient's temperature reached 102° F., the second day 103° F., the third day 102° F.; then the temperature spiked for 17 days ranging between 99° F. and 102.4° F. She had developed thrombophlebitis of the right leg. After 17 days the temperature remained normal, pain and edema of the leg subsided, and the patient was discharged with her baby seven days afterwards.

Pathological Diagnosis: Placenta accreta with rupture of the uterus.

UTERINE APOPLEXY FOLLOWING AN ELECTIVE SECOND CESAREAN SECTION*

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THAT uteroplacental apoplexy is not an infrequent condition, is shown by the fact that in four years preceding the appearance of Williams' article in 1915, twenty such cases had been described and Portes was able to collect 73 cases in 1923. In 1921, Wilson reported a series of 69 cases, 46 of which were observed at laparotomy or autopsy. In 55 cases, in which something definite is said regarding the presence or absence of clinical evidence of toxemia, the condition of the patient indicated its absence in seven cases. There were 38 maternal deaths in the 69 cases—a mortality rate for the whole series of 55 per cent. The five babies which survived were all delivered by cesarean section.

The hypothesis which Wilson advances is that a hemorrhagic toxin is liberated by the placenta, which produces its maximum effect locally, and secondarily produces manifestations of a general toxemia.

The case of uterine apoplexy which I am reporting is unique for the following reasons: First, the uterine apoplexy followed an elective secondary cesarean section in a normal patient. Second, there was no evidence of any premature separation of the placenta, and a microscopic section from the placental site did not show hemorrhage.

Mrs. E. C., Grav. ii, para i, aged 31 years. Patient always well, except for appendectomy in 1938.

Her first pregnancy was in July, 1940. This was uneventful, except that the patient was due on June 20th, and did not enter the hospital until she was four weeks overdue, at which time she had a transverse presentation. A low classical cesarean section was performed under gas oxygen and ether. The baby was abnormal and lived only a few minutes. The post-partum x-ray diagnosis on the baby was achondroplasia. The autopsy diagnosis was chondrodystrophia fetalis.

The uterine bleeding at the time of the cesarean section was moderate and controlled by intrauterine pituitrin and intravenous ergotrate.

The patient became pregnant again in July, 1941, being due April 26, 1942. She had a normal blood pressure and urine throughout her prenatal course. She was admitted to the hospital on April 12th, two weeks before term because of pain in the lower abdomen. Examination at that time showed either a small incisional hernia or a very thin uterine scar, which was slightly tender. There were no uterine contractions, the uterus was soft, membranes intact, no vaginal bleeding, vertex presentation. The baby seemed to be average size.

Blood pressure was 110/84, temperature 98.4° F., pulse 88, urine negative, hemoglobin 85 per cent, 4,200,000 red cells. Patient was given morphine and blood taken for typing and an x-ray of the abdomen showed no abnormality of the fetus.

The morphine relieved the lower abdominal pain and there were no signs of labor or recurrence of pain.

A low classical secondary cesarean section was performed the next morning, under spinal anesthesia, using 15 mg. of pontocaine and 50

*Presented before the Associated Physicians of Long Island, at Methodist Hospital, January 30, 1943, and the Brooklyn Gynecological Society, March 5, 1943.

mg. of procaine. Indications for the section were a previous cesarean section, with a thin uterine scar.

Operation was as follows: The skin incision was excised. Several areas in the fascia had separated following the previous operation. The uterine scar was well healed except in one small area where it was less than a centimeter thick. The uterine incision was made in the region of the old scar. The membranes were ruptured at this time; a normal baby girl was extracted from an L.O.T. position, weighing 6 pounds 5 ounces. The uterus remained contracted and there was no bleeding until the placenta was removed and then only a moderate amount. One c.c. of pituitrin was injected into two different areas of the uterus. The uterus was closed and the incisional hernia repaired. Duration of the operation was 55 minutes.

During the closure, the anesthetist reported that the patient's blood pressure had dropped to 80/60 and that the pulse had increased to 140. The patient was given ephedrin and 500 c.c. of plasma and kept on the operating table for further observation. She continued to remain in a shocked condition and so continuous plasma with adrenal cortex was given and arrangements were made for a blood transfusion. The anesthetist did not feel that the condition was due to spinal shock, because of its delayed appearance and because the spinal anesthesia was wearing off and never did reach a high level. A medical consultation was obtained but no evidence of chest pathology was found. Frequent examination of the abdomen did not reveal any accumulation of fluid. The uterus seemed to be enlarging. There was normal post-partum vaginal bleeding—a small amount could be expressed from the uterus. There were no clots. About three hours later the patient was still on the operating table in a shocked condition, with a blood pressure of 60/40 and pulse of 140. The abdominal dressing was removed and found to be stained with serous sanguineous fluid, but there was no evidence of any hematoma of the wound or abdominal wall. Because of the continued shock and no improvement and the pallid appearance of the patient, it was decided there must be internal bleeding, so an exploration through the abdominal incision was performed. At this time, the blood pressure could not be obtained. There was no pulse and the heart rate was about 160. Continuous plasma and blood were being given. When the incision was opened there was considerable oozing from all surfaces. The peritoneal cavity contained a considerable amount of a thin bloody fluid and there was no evidence of bleeding from the intact uterine incision. At this point the patient vomited several ounces of bright red blood. The uterus was enlarged to more than twice normal post-partum size and was purple blue in color. The wall was soft and boggy and when an attempt was made to remove it through the abdominal incision, several holes were made in the posterior wall of the fundus with the examining fingers. These areas bled considerably. A diagnosis of uterine apoplexy was made and an immediate supereervical hysterectomy performed. There was considerable oozing from raw surfaces which was controlled with suture ligatures. The patient received altogether 1,750 c.c. of 25 per cent glucose, 7 c.c. of adrenal cortex solution. The patient was on the operating table from 9 A.M. to 5 P.M. that afternoon, at which time she was very much improved, with a blood pressure of 100/60 and a pulse of 120. She received another 500 c.c. of blood upon returning to her room. She had an uneventful recovery, being discharged home, with the baby, on the nineteenth postoperative day.

Examinations since have found her to be perfectly normal.

Gross Pathological Examination of the Placenta and Uterus

The placenta showed no pathology.

Examination of the uterus showed an incision 12 cm. long. The edges of the incision were closely approximated with sutures. No fluid or clotted blood was present in the wound. The entire serosal surface of the uterus was a deep purplish-blue in color. Throughout the uterus the myometrium was deep red in color and appeared to be extensively infiltrated with blood. There were a few small clots adherent to the placental site on the posterior surface of the uterus.



Fig. 1.—Placental site—Decidua and endometrium of pregnancy. Note absence of hemorrhage in myometrium. $\times 70$.

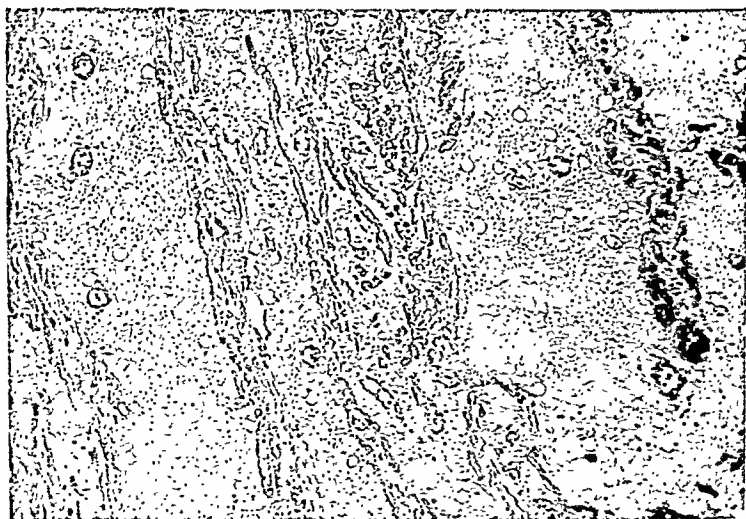


Fig. 2.—Section from outer uterine wall in the fundus. Muscle fibers widely separated by hemorrhage and edema. $\times 75$.

Microscopic examination of a section from the fundus showed muscle fibers hypertrophied and some degenerated. Single muscle fibers were separated from each other by edema and extravasated red blood cells. A section from the wall of the placental site showed a layer of blood on the inner surface, beneath this a thin zone of decidua and endome-

trium of pregnancy. The muscle fibers were hypertrophied. There was no blood in the myometrium of that area.

A section taken from the lower uterine segment showed edema and hemorrhage, but not as marked as at the fundus.

Pathological Diagnosis: Apoplexy of the uterus.

Comment

In reviewing, one case reported by Snowden showed bleeding from the abdominal incision for several days following a cesarean section in a case of uteroplacental apoplexy with nephritic toxemia.

There were numerous cases which had bleeding from other organs, and in some the intraperitoneal fluid was mostly of a serous nature.

Blood examination of the patient before and after the operation did not reveal any dyscrasia.

It seems that the uterine apoplexy in this case might have been caused by a placental toxin as described by Wilson, because of the bleeding from the abdominal incision, the vomiting of blood, the serous sanguineous fluid in the abdomen and the excessive bleeding at the time of the hysterectomy.

Conclusions

1. A review of the literature fails to reveal a similar case of uterine apoplexy.

2. This case report seems to bear out the theory that a hemorrhagic toxin may be responsible for uterine apoplexy and bleeding in other parts of the body.

3. Uterine apoplexy should be considered in patients going into marked shock following a cesarean section.

4. This case shows that a patient in extreme shock from uterine apoplexy with an unobtainable blood pressure, will withstand a hysterectomy if proper supplementary treatment is given by plasma and blood during the operation.

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34 PROSPECT PARK WEST

CHORIONEPITHELIOMA WITH REGRESSION OF THE PRIMARY UTERINE TUMOR

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THE presence of a chorionepithelioma in extragenital organs without evidence of a primary lesion in the uterus has led to several theories regarding the origin of the tumor. Among these are: (1) The tumor represents a malignant teratoma; (2) the trophoblastic emboli occurring during normal pregnancy undergo malignant transformation; and (3) the primary tumor of the uterus completely regresses while the metastatic cells find more favorable growth conditions in distant organs. With a history of pregnancy the last theory would seem most reasonable, and the case reported here lends support to that contention.

Case Report

A 22-year-old white woman, a nullipara, delivered a normal male infant at term on May 28, 1942. The gestation and delivery were normal. The placenta was normal to gross examination, but it was not submitted to the laboratory for microscopic study. The patient's post-partum course was uneventful, and the patient was discharged from the hospital ten days following delivery. She was seen six weeks later for a routine post-partum examination. At that time she had no complaints, and pelvic examination revealed no abnormalities.

On August 26, 1942, the patient was admitted to the hospital because of complaints of progressive weakness, intermittent chills, and fever, all of which had been present for two weeks. On examination the temperature was 102.6° F., pulse 120, respirations 30, and blood pressure 118/68. A faint systolic murmur was heard at the apex. The lungs were clear. No abdominal masses could be palpated. Pelvic examination showed no abnormalities. Laboratory examinations showed the hemoglobin 9.5 Gm., red cell count 3,000,000, and white cells 12,800, of which 90 per cent were mature polymorphonuclear neutrophils. The urinary examination was essentially negative. The blood Kahn test was negative. Blood smears were examined for malarial parasites, but none were found. Agglutination tests for undulant fever, tularemia, typhoid fever, and paratyphoid fever were within the normal range. Repeated blood cultures showed no growth. X-ray examinations including a chest plate, a gall bladder series, and a flat plate of the abdomen showed no abnormalities.

During the first ten days in the hospital the patient had an elevated temperature with fluctuations between 99° F. and 104° F. Therapy at this time was entirely symptomatic, consisting of iron by mouth and blood transfusions. Since the patient improved gradually, she was discharged from the hospital on September 9, 1942.

She was readmitted to the hospital on September 20, 1942, because of increasing weakness and marked tenderness in the right upper quadrant. The only positive physical finding in addition to an elevation in temperature was tenderness in the right upper quadrant. The

liver could be palpated 5 cm. beneath the costal margin. Free fluid was present in the abdominal cavity. The hemoglobin was now 7 Gm., the white cells 15,000, and the neutrophils 78 per cent. The Friedman test was not done. The patient was again given blood transfusions, but she continued to fail rapidly and expired on September 25, 1942.



Fig. 1.—Metastatic tumors of the liver.

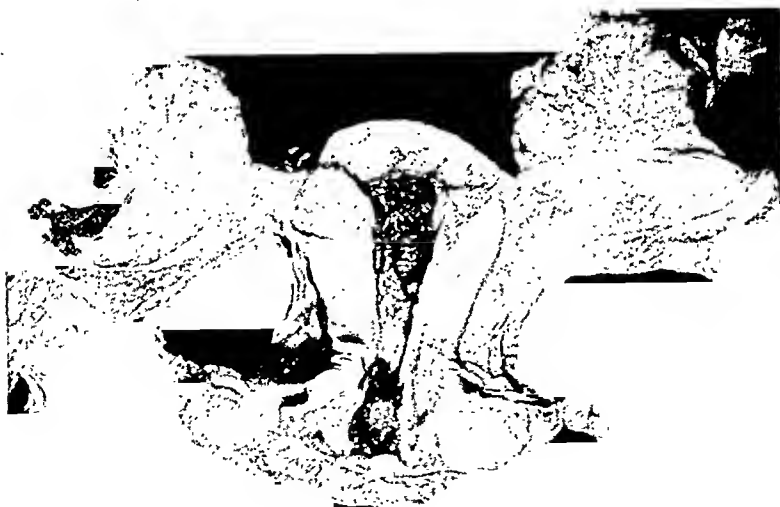


Fig. 2.—Uterus. Note hemorrhagic mass in the fundus.

Autopsy Examination.—The body was that of an adult white female measuring approximately 152 cm. in length and weighing about 100 pounds. There was no edema or jaundice. Opening of the abdomen revealed several thousand cubic centimeters of clotted and unclotted blood in the peritoneal cavity. The loops of bowel were smooth and shiny. The liver extended 5 cm. below the xyphoid and 4 cm. below the costal margin in the right anterior axillary line.

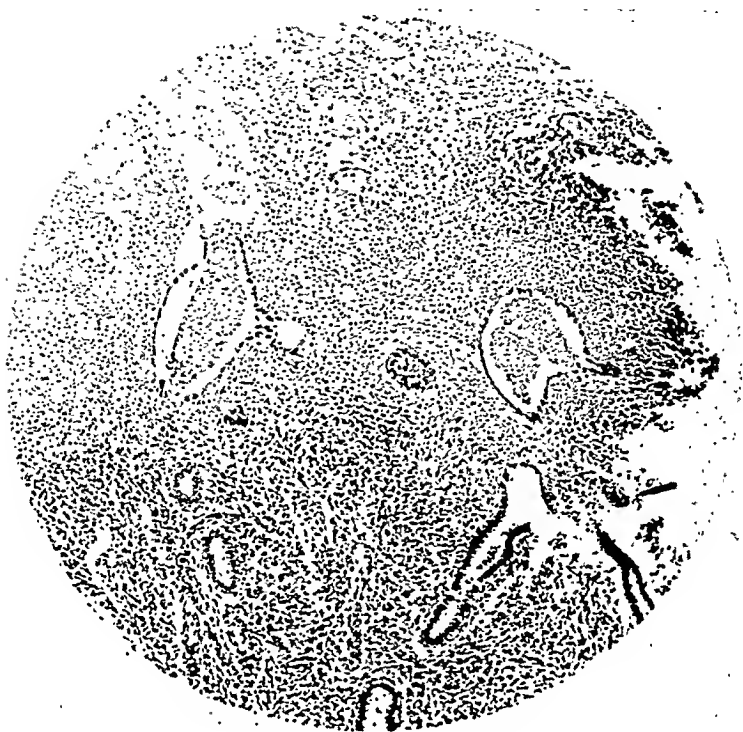


Fig. 3.—Section through the mass of uterine fundus. $\times 100$.



Fig. 4.—Section of tumor of the liver. $\times 100$.

Opening of the thorax revealed the right lung free, the left lung adherent by a few fibrous tags at the apex. The left pleural cavity contained a few cubic centimeters of blood; the right pleural cavity was empty. The pericardial sac was normal. The heart weighed approximately 300 Gm. The valves, the coronary arteries, and the myocardium were normal. The left lung weighed approximately 700 Gm.; crepitation was somewhat reduced throughout. A rather large amount of fluid exuded from the cut surface. No tumor nodules were seen. The right lung weighed approximately 500 Gm.; it presented a similar appearance.

The liver weighed approximately 2,500 Gm. A large tumor mass could be seen beneath the capsule of the right lobe, and several perforations of the capsule were present on the anterior surface; these measured several centimeters in diameter, and numerous blood clots were present in them. Examination of the cut section revealed the right lobe of the liver almost replaced by a very large tumor mass bulging from the cut surface and measuring 15 cm. in diameter. It was deep red in color, soft, and friable. The center was excavated and contained a large amount of blood. The tumor was sharply separated from the surrounding liver parenchyma. Several smaller similar nodules about 1.5 cm. in diameter were seen adjacent to the periphery of the tumor. The remainder of the liver was normal to gross examination. The empty gall bladder and the extrahepatic biliary ducts showed no abnormalities; nor did the spleen, the kidneys, the adrenals, and the pancreas.

The uterus measured 7.5 cm. in length and 4 cm. in its greatest diameter; its surface was smooth. The cervix was firm and white in color. A small amount of mucus exuded from the cervical os. Opening of the uterus revealed the endometrium to be thin, and the endometrial cavity to be normal in size. In the fundus there was a raised soft hemorrhagic mass measuring 2 cm. in diameter and 1 mm. in thickness. On palpation it was extremely soft in consistency and grossly did not appear to penetrate the uterine wall. The Fallopian tubes were normal in size. The broad ligament showed no abnormalities save for numerous thrombi which protruded from the cut vessels. The ovaries measured approximately 3.5 cm. in diameter; their surfaces were smooth and white save for several small cysts which bulged beneath the capsules. Examination of the cut surface revealed in each ovary a number of small cysts measuring 1 cm. in diameter. They were filled with clear fluid. The linings of these cysts were smooth.

The aorta was smooth throughout. The gastrointestinal tract showed no abnormalities. Permission for examination of the brain was not obtained.

Microscopic Findings.—Blocks of tissue were placed in 10 per cent formalin for fixation, embedded in paraffin, and the sections stained with hematoxylin and eosin.

Sections from the tumor mass of the liver revealed the central portion to be made up of necrotic material, fibrin, and large masses of free red blood corpuscles. The thin walls of the numerous vascular spaces coursing through the tumor were fairly well preserved. Only at the edge of the tumor could one identify viable trophoblastic cells; these showed marked pleomorphism. Most numerous were those with a spongelike, slightly eosinophilic cytoplasm and rounded vesicular nuclei containing coarse clumps of chromatin. Less common were cells

with a deeper-staining acidophilic cytoplasm and hyperchromatic nuclei irregular in shape but tending to take a spindle form. Numerous intermediate cellular types were found, and a few cells showed mitosis. Only after considerable search could multinucleated cells be found. The trophoblastic cells were found around and within the abundant vascular spaces present. Single cells could be seen in adjacent dilated sinuses or pushing into the hepatic cells. This invasive process produced atrophy and necrosis of the adjacent liver parenchyma. Here numerous leucocytes consisting of polymorphonuclear neutrophils, small lymphocytes, and plasma cells were found about the invading tumor cells. No teratomatous areas were seen in the numerous sections which were examined.

Numerous blocks were taken from the lungs, but careful search revealed no trophoblastic tissue. Unfortunately sections were not obtained from the parietal pleura. Several lymph nodes found adjacent to the aorta were normal. Examination of sections taken from the heart, the spleen, the adrenals, and the kidneys showed no abnormalities.

After fixation serial transverse sections about 1 mm. in thickness were made of the entire uterus, and the prepared sections were placed on slides in order that the entire uterine wall could be examined. Examination of the sections in approximately the midportion of the uterus showed the endometrium to be thin with only the basal layer preserved. It further showed a mild decidual reaction. The vessels of the uterine wall showed retrogressive changes with marked proliferation of the intima, narrowed irregular lumens, and a deposit of homogeneous hyaline material beneath the endothelium. Careful study of the vascular lumens and the entire uterine wall revealed no trophoblastic cells. The hemorrhagic mass seen on gross examination proved to be partially necrotized and contained shadows of decidual cells. Vessels containing viable red blood corpuscles and some endometrial glands were partially preserved. The hemorrhagic, seminecrotic mass replaced both the basal layer of the endometrium and the superficial portions of the muscularis. This mass undoubtedly represented the site of placental implantation which had undergone progressive necrosis and complete regression of trophoblastic tissue.

Sections taken from the round ligaments, the uterine tubes, and the broad ligaments were made at intervals of 5 mm. Examination revealed no trophoblastic tissue. The vessels of these structures contained numerous partially organized thrombi. Numerous sections of both ovaries were prepared for examination. A few of the cysts present were atretic follicles; in most of the cysts a thin strip of easily separated cells covered a nodular or uniformly thickened layer of cells showing luteinization. The cytoplasm of the latter group was vacuolated and stained faintly with eosin. The nuclei were dark-staining and usually rounded. These cells would seem to represent paralutein cells of the theca interna. A few small follicles showed a well-preserved granulosa layer, but none showed evidence of luteinization. Numerous corpora albicantia were seen in the ovarian stroma, but no decidual masses could be found.

Discussion

The genesis of extragenital chorionepitheliomas has provoked the interest of clinicians and pathologists. In a recent report Berman¹ summarized seventeen cases recorded in the literature as extragenital chorionepitheliomas on which autopsies had been performed. In most

of the cases a history of pregnancy was noted although the interval between pregnancy and death varied from months to years. It has been accepted that these tumors may represent a singular development in malignant teratomas, but the failure to demonstrate teratomatous elements casts doubt on the evidence.

Metastasis of chorionic tissue during normal pregnancy has been observed, and it has been suggested that such chorionic tissue may develop malignant tendencies. If this be true, one would expect to find chorionic tumors developing during the course of a normal pregnancy, and one might demonstrate multiple, somewhat uniform tumors in each lung. Such demonstrations are yet uncommon.

Novak and Koff² reported an instance in which the patient died of a metastatic chorionepithelioma, but at autopsy no trophoblastic tissue could be found in the uterus. They suggested that the primary tumor of the uterus had undergone regression while the metastatic portion had grown rapidly in other organs.

The uterine fundus in our case contained a small hemorrhagic mass but was free of chorionic tissue. This mass apparently represented abnormally retained placental tissue that may have served as the situs locum of the uterine tumor. Therefore, it is likely that the tumor of the liver in our case was metastatic in origin and that the primary uterine tumor completely regressed. The failure to find trophoblastic tissue in the uterine vessels or in the veins of the broad ligaments should not argue against the above thesis. Although this theory is based on incomplete evidence, there are few findings that would support alternate theories. If our patient had survived longer, it is probable that the uterus would have been normal while additional multiple metastatic tumors would have been present at death.

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Beruti believes that one-third of a million women die every year from childbirth throughout the world. In Argentina between 2,100 and 2,200 women die annually. At the Eliseo Cantón there were 61,684 births during the last 40 years. There were 821 maternal deaths of which 78.2 per cent were due to obstetric and 21.8 per cent to nonobstetric causes. The total maternal mortality rate was 13.3 per 1,000 births. However, while it was 22.1 per 1,000 from 1901 to 1910, it was only 5.6 per 1,000 from 1931 to 1940.

The author discusses the causes of death and emphasizes the dangers of toxemia, hemorrhage, trauma and infection.

J. P. GREENHILL.

ON THE USE OF THE WILLETT CLAMP FOR SCALP TRACTION IN DELIVERY

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IN JANUARY, 1941, one of us (H. B. McN.),¹³ published a preliminary report about the use of the scalp clamp in obstetrics, in which were presented 23 cases. Since then the scalp clamp has been used 71 times in the obstetric services of the University and Baltimore City Hospitals. This report concerns both series.

Willetts first reported his experience with the fetal scalp clamp in 1925. He apparently did not follow up his original report. The number of reports has been small and sporadic with the majority in the foreign literature. The use of the clamp has never been very popular in this country, however, it is our opinion that it represents decided advantages in certain cases over other known methods and deserves a great deal more attention than it has received.

There has been a number of instruments devised for the purpose of scalp traction. Willett originally used a Mantel's forceps which was modified to the one which now bears his name. De Lee suggested a modification of the latter, but believed that an ordinary vulsellum or myoma forceps sufficed. Gauss devised an entirely new clamp. In this series a variety of these instruments was used largely as a matter of experimentation. In the majority of cases an ordinary hemorrhoid clamp proved quite satisfactory.

The forceps must have a fairly long handle and a T-shaped bite of sufficient width and firmness to insure a secure grasp. Serrated teeth may cause more serious and much more frequent scalp injuries, and they are not necessary to secure a firm bite into the scalp.

The technique is simple and may be used in the primigravida or the multigravida. When the membranes are ruptured (with the instrument itself, if desired) and the cervix is sufficiently dilated to allow for the introduction of the clamp, it is inserted under the guidance of the fingers and attached to the scalp of the fetus as near the occiput as possible. If the head is floating it may be necessary to exert pressure upon the fundus or lower uterine segment to maneuver the head into a position favorable for grasping. After it has been made secure there is attached to the clamp a tape or length of gauze which runs over a pulley at the edge of the bed and to which is fastened, in turn, a one-fourth to one-half pound weight that is held in suspension. This weight should not be greater than specified or heavy enough to cause damage on the maternal soft parts, but sufficient to hold the head against the lower uterine segment and thus irritate the uterus to greater activity. Although some writers claim that the instrument should be removed after 6 hours or after the head is engaged in the pelvis, it has been the authors' experience that it may remain safely in place until the second stage is completed, or a maximum of about 12 hours, the usual time of removal being when delivery was imminent.

We have used the scalp clamp in the following types of cases:

1. *Placenta Previa*.—It is used only in the marginal and partial types to tamponade the bleeding points as well as hasten labor by virtue of

the irritation of the lower uterine segment. This procedure offers a satisfactory substitute for cesarean section. It does not present the danger of infection of the Braxton Hicks bipolar version. The hydrostatic dilators frequently introduce infection and dislodge the presenting part, thereby increasing the possibility of prolapse of the cord or malpresentation. The clamp produces the desired results more efficiently and more simply.

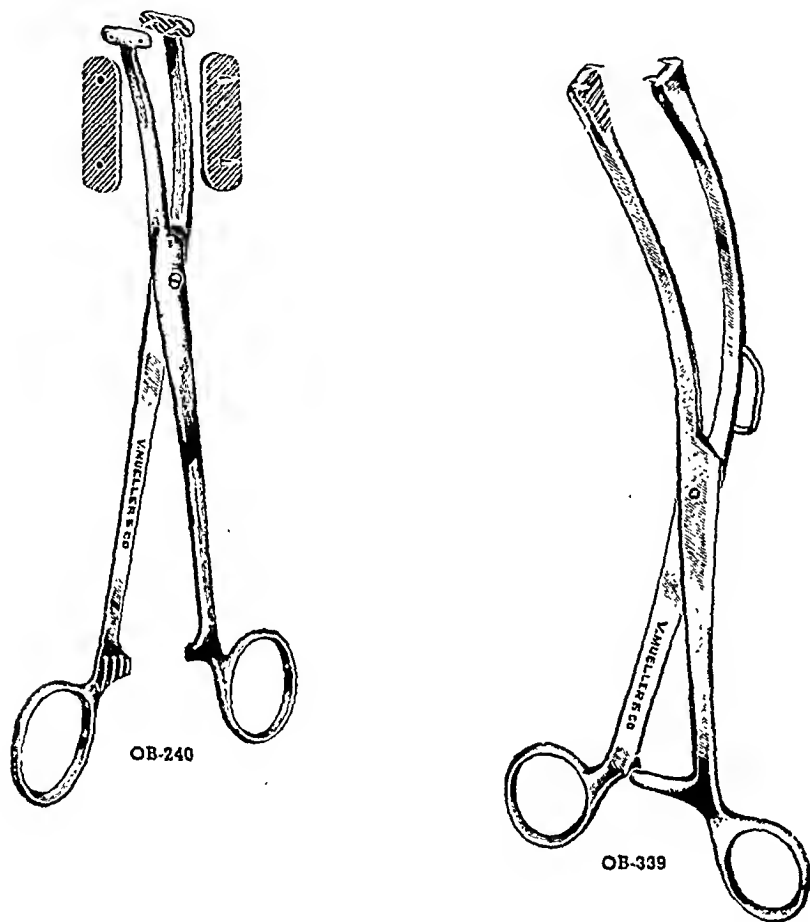


Fig. 1.

2. *Premature Separation of the Placenta.*—Particularly in the low implanted variety and in some selected cases of the normally implanted placenta. The mechanism is essentially the same as with placenta previa. The Spanish windlass probably should be reserved for a few selected cases in which hemorrhage is an outstanding feature, or in combination with the clamp.

3. *Uterine Inertia.*—It has been found that the traction force of this method brings the head in close contact with the lower uterine segment and stimulates the uterus to contract normally. This method removes, in many cases, the necessity for the administration of oxytocic drugs, some of which have the tendency to further tire the uterus, whereas the gentle direct mechanical stimulation does not force the uterus beyond its normal contractile capacity.

4. *Induction of Labor.*—The mechanism is the same as described for uterine inertia.

5. *Malpresentation of the Vertex*.—Such cases may be corrected by vaginal or combined manipulation and the attachment of the scalp clamp to a portion of the fetal scalp at or near the occiput. The traction will insure the permanency of the newly converted position and thus provide relief from possible dystocia caused by the positional disproportion.

6. It may be applied to the floating head when the membranes are ruptured to prevent the prolapse of the fetal parts or cord.

7. Finally, this method can be used in cases of known fetal death to hasten delivery when this is indicated. Craniotomy and forceful extraction of the child is certainly less desirable than scalp clamp traction with the relatively small amount of manipulation that is required. The latter method does not involve as much initial cervical dilatation, and does not injure the birth canal or subject the patient to as much risk of infection.

Table I presents the indications for which the scalp clamp was used in this series of 94 cases. Ante-partum and intrapartum hemorrhage was the indication in 45 cases. One of the cases of premature separation of a normal implanted placenta was of breech presentation which was treated by external version and the application of the clamp with subsequent control of the bleeding. The average blood loss before the application of the clamp was 296 c.c. (estimated). The average bleeding afterward was insignificant, less than 10 c.c. and in 34 cases there was none.

TABLE I. INDICATION OF THE USE OF THE CLAMP IN THIS SERIES

1. ANTE-PARTUM AND INTRAPARTUM HEMORRHAGE	45
a. Partial premature separation of low placenta	22
b. Premature separation of normal implanted placenta	8
c. Cause undetermined	6
d. Marginal placenta previa	5
e. Partial placenta previa	2
f. Hemorrhage from amniotic sac	1
g. Cervical erosion at term	1
2. UTERINE INERTIA	25
3. INDUCTION OF LABOR	13
a. Hypertensive disease	3
b. Eclampsia	2
c. Fulminating pre-eclampsia	4
d. Renal disease	1
e. Hydrocephalus	1
f. Floating head with membranes ruptured	1
g. Dead fetus	1
4. TRANSVERSE ARREST	6
5. MALPRESENTATION OF THE VERTEX, CORRECTED	5

In the next largest group, uterine inertia, the character of the pains, as well as the frequency was greatly improved in 22 cases. In the other 3 cases there was no change in the character.

In the cases of transverse arrest, the clamp was used entirely experimentally and we found that it had no effect whatsoever on proper rotation of the vertex. Four of these cases were manually rotated after full dilatation of the cervix.

The five cases of malpresentations were as follows: two were anterior face presentations that were converted to occiput posteriors, with excellent results. One was a military attitude that maintained flexion after correction. Two were compound presentations of the head and the hand and, after correction, continued on in labor normally.

In this series there were 33 primigravidas and 61 multigravidas. The average parity was 2.6.

The average duration of the latent period between the application of the clamp and the onset of labor in 38 cases was 1 hour and 24 minutes. The average duration of labor in these cases was 10 hours and 31 minutes. Of those already in labor, the average duration of labor before the application of the clamp in 56 cases was 34 hours and 40 minutes with the average cervical dilatation 4 cm. The number of cases which had prolonged labor, that is to say over 30 hours, in this latter group was 33. The average duration of labor in this group after the application of the clamp was 9 hours and 8 minutes.

The mode of delivery was as follows: Low or control forceps, thirty-one; midforceps with hysterostomy, five; midforceps alone, four. It should be stated that control forceps is a routine procedure in these clinics. Of the five midforceps with hysterostomy, one must be deemed a failure, two were definite cases of cephalopelvic disproportion, and two were cases of transverse arrest. Of the other four midforceps, two must be deemed failures while the other two again were cases of cephalopelvic disproportion. The three failures were with uterine inertia.

The membranes had ruptured spontaneously before the application in 30 cases, and an amniorhexis for induction had been done in 6 cases. In these 6 cases labor did not follow and the clamp was applied. In these 36 cases the total morbidity was 27.77 per cent. In the 58 cases in which the membranes were artificially ruptured at the time of application of the clamp, the morbidity was 27.58 per cent. Considering the complications that indicated the use of the scalp clamp, we do not think this figure is excessive. There were 4 cases in which there were febrile courses and complications other than birth canal. There was no maternal mortality.

The complications to the fetal scalp were as follows: cellulitis, 9, all survived: abscess of the scalp, 2, all survived: hematoma, 2, absorbed: laceration, 8, all healed.

There were 13 term stillbirths and 3 premature stillbirths, two term neonatal deaths and 8 premature neonatal deaths, a total of 26 deaths or a fetal mortality of 26.80 per cent. There were 25 premature births

TABLE II. STILLBIRTHS AND NEONATAL DEATHS

TERM STILLBIRTHS		13
Cephalopelvic disproportion	4	
Hypertensive disease, severe, maternal	2	
Macerated, cause unknown	2	
Prolapse cord and maceration	1	
Premature separation of normal implanted placenta	2	
Premature separation of low implanted placenta	1	
Hydrocephalus	1	
TERM NEONATAL DEATHS		2
Pneumonia, lobular; eclampsia, maternal	1	
Suprarenal hemorrhage, severe	1	
PREMATURE STILLBIRTHS		3
Premature separation of normally implanted placenta	2	
Prolapse of cord	1	
PREMATURE NEONATAL DEATHS		8
Premature separation of low implanted placenta	4	
Premature separation of normally implanted placenta	1	
Hemorrhagic disease (before vitamin K)	1	
Partial placenta previa	2	

and 3 sets of twins. This high fetal death rate is clarified in Table II. The four cases of cephalopelvic disproportion were in labor a long time before hospitalization. In the two cases of prolapse of the cord, the fetuses were already dead on admission to the hospital. In the cases of bleeding in which the children were either stillborn or died after birth, the average amount of blood loss was about 500 c.c.

Summary and Conclusions

1. The Willett clamp application to the fetal scalp offers definite advantages over other generally used methods of treatment in certain cases of placenta previa, premature separation of the placenta and uterine inertia. It is of definite value in the induction of labor, in the prevention of prolapse of the cord or of fetal parts, and in the maintenance of correction of malpresentations of the vertex.

2. Ninety-four cases are presented with 9 failures, 6 were experimental in transverse positions of the vertex, the final outcome consisting of 2 midforceps with hysterostotomy and 4 manual rotations with low forceps. There were 3 failures with uterine inertia. All three were delivered by midforceps, in one of which hysterostotomy was used.

3. This method has no particular value in the treatment of transverse positions of the vertex.

4. Risk to the baby is minimal.

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AXIAL TORSION OF THE GRAVID UTERUS IN TWO SUCCESSIVE PREGNANCIES

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TORSION of the pregnant uterus is not a common occurrence but has been reported in a sufficient number of cases to make its diagnosis possible and yet, surprisingly, most diagnoses have been made at the operating or autopsy table. Physiologic rotation of the pregnant uterus has been seen at the time of cesarian section and torsion of the gravid uterus in cattle described first by Hippiaper Columbi in 1662, the predisposing cause being bicornuate uterus with its absent round and broad ligaments on one side, has been mentioned by Eastman¹ and others. In the human being torsion of the pregnant uterus has been described early in pregnancy due to mobilizing adhesions,² at term, in labor and in the post-partum period. Pathologic conditions of the uterus (fibromyomata) and interstitial pregnancy,³ and tumors of the ovary are in most instances believed to be the exciting cause but, as Vogel⁴ states "most writers emphasize the presence of ptosis with asthenia." The endopelvic fasciae and ligaments of the uterus in the normal healthy individual are capable of tremendous strain without allowing extreme degrees of rotation of the uterus in spite of such complicating pathology as tumors and adhesions. The asthenic type show nutritional defects in muscles and ligaments throughout the body as well as in those of the pelvic structures, so that, is it not fair to assume that postural changes, sudden straining, tumors, adhesions or interstitial pregnancy, may be the insult which carry through to a greater degree the physiologic rotation and then labor completes the axial torsion.

Rotation may be either to left or right, but most of the reported cases were clockwise and the degree of rotation has been from 90 to 360 degrees. Von Pall³ mentions Schweigl's reported case of pregnant myomatous uterus with torsion of 540 degrees in which the body of the uterus was necrotic.

The symptoms associated with torsion are dependent on the degree and the rapidity with which it occurs. Day⁵ in his review of the literature up to 1935 has in detail covered the symptoms of shock, abdominal pain and abnormal findings on examination and suggests that no attempt be made to reduce the torsion by external manipulation. However, he cites a case quoted to him by a colleague who was able to rotate a fibromyoma from right to left in a patient who was in labor, immediately relieving the patient's symptoms and allowing the labor to terminate spontaneously. This case alone should lead us to attempt replacing the uterus into normal position if the diagnosis is made, using anesthesia when possible. It is well, however, to remember that premature separation of the normally implanted placenta may be a concomitant finding, that rupture of the peritoneal covering of the uterus has been known to occur and that fatal embolism has resulted from detorsion.⁵ Certainly, if reduction is attempted gentleness should be the watchword with the patient prepared for cesarean section if the attempt results in failure.

It is impossible to propose any set procedure. The type of cesarean must be dependent on the pathology and in the patient here cited, in whom axial torsion occurred in each of her two pregnancies, the treatment had to be guided by many factors.

Mrs. A. W., 38 years of age, was first seen November 14, 1940, when she was approximately 16 weeks' pregnant. (Last menstrual period July 23, 1940; expected date of confinement April 30, 1941). She had married in April, 1940, had never consulted a physician "for any illness" previous to the pregnancy and her past history, menstrual history and course of this pregnancy were not remarkable, her usual weight being 130 pounds and height 67 inches. She was of the slim asthenic type and poorly nourished. Her blood pressure was 118/66, red blood count 3,820,000 and hemoglobin 68 per cent, white blood cells 7,600 with normal differential count, negative Kahn and Type O. The abdomen showed no scars and in spite of the fact that she was 16 weeks pregnant the fundus of the uterus was at the level of a 28 weeks' pregnancy and was nodular, palpation being easy through the thin abdominal wall. In the left side of the fundus a large soft fibroid could be palpated and its outline easily seen. No fetal heart could be heard, x-ray revealed no fetal skeleton and pelvis was the normal gynecoid type. Progress was normal, the fetal heart was constant in the right side and on April 22, 1941, the large fibroid in the left side of the fundus could be palpated protruding beneath the left rib margin. The vertex presented, was small, in midpelvis and ballotable. Her weight had increased to 149 pounds (19-pound gain), and there had been no complaints. Labor started on the night of April 24, 1941, at 8 P.M. She was admitted to the St. Vincent's Hospital at midnight and at 3 A.M. April 25, 1941, when the pains were recurring at 5-minute intervals, a rectal examination revealed the cervix to be thinning, 6 cm. dilated, vertex in right anterior position, fixed, small and at the level of the spines. Sedation was given with good results. A vaginal examination at 5 P.M. April 26, 1941, 21 hours after onset of labor revealed the head well above the spines, the cervix still 6 cm. dilated. The effect of the sedation had decreased, the patient had been more comfortable on her right side and two hours later the pains increased in intensity, became almost continuous and on rectal examination neither the head nor the cervix could be felt, the membranes being still intact. The abdomen was tense and tender and no shock was evident when one hour later cesarean was started. Torsion of the uterus was not considered but it was felt that because of the patient's age, the failure of progress in spite of strong pains, and the possibility of premature separation of the placenta, section was indicated. On opening the abdomen through a low median incision, 180 degrees axial rotation of the pregnant uterus was seen. The large intramural fibroid in the left side of the fundus was now in the right side beneath the liver, torsion having occurred through the lower segment of the uterus. The left round ligament could be followed obliquely from left to right, varicosities of the left broad ligament were markedly distended with blood and the posterior wall of the uterus, which presented in the wound, was deeply congested between the many small fibroids which studded it. The bladder was deep in the right side of the pelvis. Complete detorsion of the uterus was impossible, but with traction sutures after the incision had been extended above the umbilicus, reduction to approximately 90 degrees resulted. A longitudinal incision in front and parallel to the left broad ligament

allowed extraction of a 2,500-gram female child, meconium stained, which failed to breathe in spite of artificial resuscitation. The infant at birth was markedly cyanotic in the face, neck and extremities, with marked pallor of the chest and abdomen corresponding to the compression area. Autopsy was negative. The uterus contracted well and could be rotated to normal position after removal of the placenta which showed no evidence of premature separation. Moderate shock was evident, plasma and blood were given but the patient's condition made hysterectomy or myomectomy impossible. Eight grams of sulfanilamide crystals were sprinkled in the pelvis and suture line of the uterus and the abdomen closed. Convalescence was stormy for the first eight days, but thereafter was uneventful. The sutures were removed on the tenth day with primary union of the wound and the patient discharged on the sixteenth postoperative day.

Subsequent examinations at four- and six-week intervals showed the uterus to be about the size of a 16 weeks' pregnancy, nodular and movable. Her first menstrual period occurred on June 26, 1941, eight weeks post partum and although either myomectomy or hysterectomy was advised the patient refused because of her desire to have a child.

She was next seen June 3, 1942, again pregnant four months. Her periods had recurred regularly with normal flow and not accompanied by any discomfort. Her last menstrual period occurred on January 20, 1942; the expected date of confinement October 27, 1942. Blood examination, urine analysis and blood pressure were normal. The fundus on the left extended to the rib margin, on the right to the umbilicus. Myomectomy was suggested and refused and her progress was normal throughout the ante-partum period with regular examinations every two weeks up to the seventh month and weekly observations thereafter. The baby presented by the vertex, the fetal heart was regularly heard in the left lower quadrant and the fibroid in the fundus remained on the left side up to the visit of September 23, 1942, one month before term. From this date rotation of the uterus from left to right was gradual, the fetal heart moving from the left lower quadrant to the midline. The fibroid in the left moved toward the midline and could be felt in the right side. Notwithstanding the gradual torsion the patient experienced no discomfort. The patient was sectioned on October 21, 1942, one week before term, after failure at detorsion by external manipulation. Porro section or myomectomy was to be performed if her baby was normal. On opening the abdomen after excision of the scar, the pregnant uterus was seen in 90 degrees torsion, the uterus was incised just anterior to the broad ligament through the previous incision which was well healed and a 2,400-gram female child delivered. Examination of the infant revealed congenital absence of the roof of the mouth, including both the hard and soft palate. A small tab of tissue was noted between the upper and lower alveolar arches on the right side. The upper alveolar arch was very thick and there was marked hypoplasia of the mandible. The slitlike openings of the nasal canals were clearly visible. The child presented a severe feeding problem, developed bronchopneumonia and expired when 7 days old.

The report of the examination of the baby on delivery excluded all possibility of hysterectomy or myomectomy. Reluctantly the abdomen was closed, her convalescence was normal and she was discharged on her fourteenth postoperative day. When she was seen for final discharge the uterus was the size of a four months' pregnancy, her menstrual periods were normal and there were no complaints.

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130 EAST 67TH STREET

Beruti, J. A.: *The Future of Forceps and the Forceps of the Future*, *Obst. y Ginec. Latino-Americanas* 1: 10, 1943.

At the Eliseo Cantón in Buenos Aires, 35 per cent of all the operations performed during the last 40 years were forceps deliveries. In addition the incidence of internal version was 12.8 per cent, of abdominal cesarean section 4.7 per cent and of pelviotomy 3.9 per cent. The frequency of forceps operations decreased from 38 per cent in the decade 1921 to 1930 to 33.7 per cent during the years 1931 to 1937, whereas cesarean sections increased from 4.6 per cent to 11.4 per cent. The author maintains that the incidence of forceps delivery has decreased because of the greater use of cesarean section. He believes that in the near future vaginal operations will completely disappear. There is no perfect type of forceps and because of it the maternal and fetal mortalities are high. The author prefers the straight Zweifel forceps to any axis-traction forceps because by means of a uni- or bilateral episiotomy the birth canal is straightened out and there is no need for axis traction. To overcome the defects of the straight forceps the author has perfected a forceps which he calls "Polimorfo" and which can be used as a straight instrument for rotation and a curved one for extraction. He maintains, however, that the future for forceps is not promising and that we must try to find an instrument which is less dangerous to the mother and child.

J. P. GREENHILL.

Hawk, M. H., and Wangeman, C. P.: *The Effects of Nembutal (Sodium Pentobarbital) and Scopolamine on Human Subjects*, *Anesthesiology* 4: 238, 1943.

Nembutal (sodium pentobarbital) is a popular sedative with both the medical profession and the lay public. This drug has very definite stimulative and depressant qualities. In combination with morphine or scopolamine it exhibits these qualities in various ways. For example, the addition of scopolamine lessens the depressing effects of nembutal. "This is particularly true with respect to minute volume exchange of air to and from the lungs. There is less depression of the respiratory functions with nembutal than with morphine. The combination of nembutal and scopolamine causes less respiratory depression than that caused by morphine and scopolamine. The addition of scopolamine to nembutal provides a less profound, longer acting and more pleasant sedation than nembutal alone in spite of the apparent greater restlessness."

The combination of nembutal and scopolamine works very satisfactorily and is recommended for preoperative sedation. It is an excellent inhibitor of mucous secretion. It is not recommended as a pain reliever.

HARVEY B. MATTHEWS.

Editorial

Precision Methods in Cephalometry and Pelvimetry

THE recent publication of a simple method of cephalometry and pelvimetry* suggests speculation in a subject in which the fields of roentgenology and of obstetrics are intimately related and interested. Dr. Cave, author of this article, presents, as have many roentgenologists before him, another precision method which is, no doubt, quite accurate and claims to eliminate the human factor in estimating the distance of the object from the film. The method is a modification of one recorded by Portes and Blanche in 1924. Exposures are made with the same centering but with different known tube-film distances. The resultant film images are measured and applied in a special formula which gives the actual length of the diameter under consideration. In pelvimetry the author claims that it can be employed to any transverse diameter of the inlet or outlet. However, it should be emphasized that with this method of pelvic mensuration, as well as with others, unless contour studies of the pelvis are combined, the greatest usefulness of roentgenography to clinical obstetrics will be overlooked.

In considering any precision methods of roentgen pelvimetry, we should not forget just exactly what they mean. They simply represent the relationships of the bones of the pelvis to each other at the moment the roentgenogram was made. The obstetrician in evaluating such exact information nevertheless must realize that not only does pregnancy itself influence those relationships but the "positioning" of the patient incident to the taking of the roentgenogram also may exert a certain influence. Studies of the influence of pregnancy on the pelvic articulations are well established, while the effect of posture to cause changes in pelvic relationships is also well known. It is true that such influences probably have but minor effects, but they are present nevertheless. Precision methods of roentgen pelvimetry therefore may be accurate as far as a single roentgenogram is concerned, but they must be evaluated clinically to be essentially useful. It seems reasonable to conclude that any dimension of the bony pelvic canal which is accurate to 0.5 centimeters should be satisfactory and clinically useful.

In considering the great advantages to be offered by roentgen pelvic investigation we must not forget that from the clinical point of view, unless contour studies of the bony pelvic structure are combined with mensural information, the greatest usefulness of such studies will not be obtained.

*Cave, Paul: *Brit. M. J.*, August 14, 1943, p. 196.

Therefore, in considering evidence offered by roentgenography, the obstetrician must have in mind not only what the bony pelvis looks like but he should know something of the so-called "normal" variations of this structure. That these variations may have a definite influence on the course of labor has become established largely through the contributions of our American investigators. We should again remind those working in roentgenologic fields that if methods of pelvimetry are complicated and the interpretation largely in the hands of the roentgenologist, the usefulness of the information so obtained is going to be limited and the whole subject of roentgen pelvimetry become somewhat mystifying to the obstetrician. Unless films can be viewed and evaluated by the obstetrician himself, and unless he alone is to be responsible for the solution of his clinical problems, conflicts will arise which will impede the essential usefulness of the greatly valuable knowledge which roentgenography is now able to offer.

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Department of Statistics

A SURVEY OF ABORTION DEATHS IN PHILADELPHIA FROM 1931 TO 1940 INCLUSIVE*

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ON MAY 23, 1934, Williams¹ reported on a "Survey and Analysis of Maternal Mortality in Philadelphia" covering 717 deaths occurring in 1931, 1932 and 1933. In the three years there were 26 nonseptic abortion deaths and 162 septic abortion deaths or a ratio of one to six. This study of 450 cases incorporates all the cases from 1931, and is a continuation of Dr. Williams' report on nonseptic and septic abortions up to and including the year 1940.

In Philadelphia, all maternal deaths are analyzed by a maternal mortality committee which determines whether the death is nonpreventable or preventable on the part of the physician or the patient. Bringing into an open discussion the causes which contributed to the patient's death has made every Philadelphia physician doing maternity work, obstetric conscious, resulting in better obstetrics, so that today the puerperal mortality rate in our city has dropped from 6.0 per thousand live births in 1931 to 2.3 in 1940.

TABLE I. PUERPERAL MORTALITY RATE FOR A TEN-YEAR PERIOD

YEAR	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940
Rate*	6.0	6.5	4.5	5.3	4.9	5.3	3.8	3.1	2.8	2.3

(*Per 1,000 Live Births).

Each case is thoroughly investigated, the attending physician is urged to attend the meeting and give his version of the case. While this postgraduate study tends to better obstetrics, in so far as reducing puerperal mortality, in abortion deaths there is the uncontrollable factor of self-induction or of having another person induce the abortion.

TABLE II. PERCENTAGE OF ABORTIONS AND PERCENTAGE OF PUERPERAL DEATHS

	TOTAL	1931	1932	1933	1934	1935	1936	1937	1938	1939	1940
Nonseptic abortion	37	10	11	3	1	5	2	1	0	2	2
Septic abortion	413	63	55	42	52	46	48	47	19	19	22
Percentage abortion deaths		29.4	27.6	29.6	32.3	32.7	28.7	41.0	19.2	24.4	31.6
Percentage of puerperal deaths		70.6	72.4	70.4	67.7	67.3	71.3	59.0	80.8	75.6	68.4

The term "abortion" is applied to cases of a nonviable fetus, that is, one of under 28 weeks of pregnancy. Over the ten-year period 1931 to 1940 inclusive, there were 450 abortion deaths, 37 cases being nonseptic and 413 cases septic, or a ratio of 1 to 11.6. In 1931 and 1932, the peak years, there were ten and eleven deaths respectively in the nonseptic group and 63 and 55 deaths respectively in the septic group; from then on there has been a gradual decline in both groups, to such an extent that the low point was reached in 1938, when there were no nonseptic deaths and in the septic cases the years 1938 and 1939 showed nineteen deaths in each year. While this is an improvement, still the abortion mortality is high as shown in the year 1937, when abortion took a toll

*Presented at a Meeting of the Obstetrical Society of Philadelphia, May 6, 1943.

of forty-eight lives or 41 per cent of the total puerperal deaths. It will be noted that the percentage of abortion deaths every year is roughly about the same, approximately 29 per cent, except in the years 1937, 1938 and 1939.

Abortion, both septic and nonseptic, in the ten years, caused a 25 per cent mortality of all puerperal deaths. There were 279 nonobstetric deaths during this decade, so, if these cases are deducted, the corrected mortality of abortion deaths in Philadelphia between 1931 and 1940 inclusive is 29.8 per cent of all puerperal deaths. In terms of births, there were 318,103 deliveries in Philadelphia both live and stillborn during the ten-year period, so that the ratio of abortion deaths is 11 per thousand total births.

TABLE III. NONSEPTIC ABORTIONS

	TOTAL	PRIMIPARA		MULTIPARA	
		MARRIED	SINGLE	MARRIED	SINGLE
Spontaneous	26	6	0	20	0
Induced	8	2	2	4	0
Therapeutic	2	0	0	2	0
Operative	1	1	0	0	0
Totals	37	9	2	26	0

In the nonseptic group of 37 cases, 35 were married and two single, the ages ranging from 23 to 46 years of age in the married group and in the single cases, there were only two, one 24 years of age and colored, the other 33 years old and white. Reduced to percentages, 94 per cent occurred in married women. There were 32 white women and five colored. There were 26 spontaneous abortions, six were primiparas and twenty multiparas, all married. Eight women induced the abortion on themselves or had someone person do it for them, four were primiparas, two married and two single, and four multiparas, married. There were two therapeutic abortions in multipara and one operative case in a married primipara with a mistaken diagnosis of ectopic pregnancy, who died on the operating table evidently from a pulmonary embolus.

The principal cause of death in this group was hemorrhage representing 23 cases or 62.2 per cent. In the septic group all cases hemorrhaged, indeed to such an extent that 31 cases were moribund on admission to the hospital.

There were fifteen abortion deaths complicated with other diseases.

TABLE IV. ABORTIONS COMPLICATED WITH OTHER DISEASES

Pneumonia	6 cases
Influenza	1 case
Pulmonary embolism	1 case
Hemorrhagic infarct following abortion	1 case
Cardiovascular disease	3 cases
Cardiac dilatation and ergot poisoning	1 case
Gastric hemorrhage	1 case
Hydatidiform mole (under hemorrhage deaths)	1 case

Pneumonia complicating abortions offers a grave prognosis. In the six cases the interval between birth and death of the mother occurred:

Three days in an early abortion,
 Six days in an early abortion,
 One and one-half hours in a three months' pregnancy,
 Six days in a three months' pregnancy,
 Eight hours and 20 minutes in a three and one-half months' pregnancy,
 Five minutes in a six months' pregnancy, and
 Seven days in a case of influenza.

The majority of the abortions, 239 cases or 53 per cent in both the septic and nonseptic groups, occurred within the first three and one-half months of preg-

nancy. Between three and one-half months and six months there were 76 cases. One hundred and thirty-five cases were classified as undetermined, but by the histories, we feel over one half of these can be placed within the first three and one-half months of pregnancy.

There were two therapeutic abortions. One a case of cardiorenal disease, the other a case of chronic nephritis both associated with hypertension. The Committee decided one case was nonpreventable, the other preventable on the part of the physician, due to an error in judgment.

The Committee determined that sixteen deaths in the nonseptic group were nonpreventable, twelve deaths preventable on the part of the patient and nine on the part of the physician. Five of these nine deaths were due to hemorrhage and could have been saved by combating shock and restoring blood volume before proceeding to evacuate the uterus.

TABLE V. SEPTIC ABORTIONS

	TOTAL	SPONTANEOUS		INDUCED		THERAPEUTIC	
		PRIMIP- ARA	MULTIP- ARA	PRIMIP- ARA	MULTIP- ARA	PRIMIP- ARA	MULTIP- ARA
Married	299	34	31	76	151	1	6
Single	97	9	3	78	7	0	0
Divorced	6	2	2	2	0	0	0
Widow	9	0	3	5	1	0	0
Separated	2	0	1	0	1	0	0
Total		45	40	161	160	1	6
	413		85		321		7

Septic abortion over the ten-year period caused 413 deaths. There were 45 spontaneous abortions in primiparas, 161 induced and one therapeutic abortion. In the multipara, there were 40 spontaneous abortions, 160 induced and six therapeutic. Three hundred and eleven women were white and 102 colored, the white outnumbering the colored by more than 3 to 1. Briscoe², in a ten-year analysis of puerperal sepsis in Philadelphia from 1931 to 1940, found a similar ratio of 3.2 to 1.

Williams, in his three-year study of abortion deaths in Philadelphia 1931 to 1933, pointed out that "one of the outstanding facts about this survey is that 22.5 per cent or over one-fifth of the total deaths studied (162 of the total 717 puerperal deaths) were caused by septic abortion." Seven years later, we can report for the ten-year period 1931 to 1940, that there is no improvement, the death rate from septic abortion being 27.3 per cent (413 of the total of 1,511 puerperal deaths) or one abortion death in every 3.6 puerperal death.

TABLE VI. ABORTION WITHOUT SEPSIS

1931	1932	1933	1934	1935	1936	1937	1938	1939	1940
10	11	3	1	5	2	1	0	2	2
TOTAL 30 cases or 81%					TOTAL 7 cases or 19%				
ABORTION WITH SEPSIS									
1931	1932	1933	1934	1935	1936	1937	1938	1939	1940
63	55	42	52	46	48	47	19	19	22
TOTAL 258 cases or 62.5%					TOTAL 155 cases or 37.5%				
(AVERAGE 71.5%)					(AVERAGE 28.5%)				

In seeking a cause for this increase, we are impressed with the fact that 81 per cent, or 30 cases, occurred in the nonseptic abortions in the first five years 1931 to 1935 inclusive, and that 62.5 per cent or 258 cases occurred in the septic group in the same period of time. In the second five-year period, from 1936 to 1940 there were 19 per cent or seven cases in the nonseptic group, and 38 per

cent or 155 cases in the septic group. In other words, abortion both septic and nonseptic occurred in 71.5 per cent during the first five-year period, compared with 28.5 per cent during the second five-year period. We feel that the financial depression was a predisposing factor in causing the increase during the first five-year period.

In this study of septic cases, there were 299 married women, 97 single women, nine widows, six divorcees and two separated, or a similar ratio of almost three married women to one illegitimately pregnant. The number of induced abortions irrespective of wedlock outnumbered the spontaneous abortions by almost four to one. There were 321 induced abortions, 85 spontaneous abortions and seven therapeutic.

Many of these septic cases were treated with sulfathiazole. We prefer sulfanilamide to any of the other sulfonamides in these infected cases, and give it early as soon as the patient develops a fever. We feel many physicians have been weaned away from sulfanilamide due to the associated cyanosis and various toxic reactions which occasionally occur. However, in septic abortions we feel none of the other sulfonamides can take the place of sulfanilamide. The cyanosis in these cases is due to methemoglobin, which can be promptly reduced from a blood level of 30 to 40 per cent to less than 4 per cent in 30 minutes by giving intravenously methylene blue 0.1 to 0.2 c.c. of a 1 per cent solution per kilo body weight. This can be repeated in 8 hours. We have for years been giving by mouth 5 gr. of methylene blue three times a day at the start of sulfanilamide treatment which effectively combats the cyanosis.^{3, 4}

There were seven therapeutic abortions, three cases of toxemia associated with hypertension, one case of placenta previa, one case of heart disease, one case of bleeding in a threatened abortion sixteen weeks pregnant, and one case of pyelitis. Including the two nonseptic therapeutic abortions, the committee decided of the nine cases, two were nonpreventable and seven preventable on the part of the physician.

TABLE VII. PREVENTABILITY

	DEATHS	NONSEPTIC	SEPTIC	PERCENTAGE
Nonpreventable	64	16	48	14%
Preventable on the part of the patient	332	12	320	73.7%
Preventable on the part of the physician	54	9	45	12%

In the whole group of 450 cases, 14 per cent were nonpreventable, 73.7 per cent were preventable on the part of the patient and 12 per cent preventable on the part of the physician. Under nonpreventable deaths are classified spontaneous abortions, the result of an unavoidable accident or cases complicated with other intercurrent diseases. Preventability on the part of the patient was due usually to self-induction or having someone induce the abortion for her, or lack of prenatal care. Preventability on the part of the physician was due, either to an error in judgment or error in technique. We feel that, in a city with five medical schools, a twelve per cent preventability factor on the part of the physician is too high.

Summary

1. Four hundred and fifty cases of abortion deaths occurred in Philadelphia during a ten-year period between 1931 and 1940; 37 cases were nonseptic and 413 cases septic, or a ratio of one to 11.6.

2. Abortion deaths represent 29.8 per cent of all puerperal deaths during this decade or in terms of total births, eleven per ten thousand total births.

3. Hemorrhage was the principal cause of death in the nonseptic group, representing 62.2 per cent. In the septic group, while all cases hemorrhaged and 31 cases were admitted to the hospital in a moribund condition, the chief cause of death was sepsis which included such terms as septic endometritis, peritonitis, septicemia, etc.

4. In this study, the death rate from septic abortion is 27.3 per cent or one abortion death in every 3.6 puerperal death.

5. In the septic cases, the ratio of married women to those illegitimately pregnant is about three to one. Induced abortions, irrespective of wedlock, outnumbered the spontaneous abortions by almost four to one.

6. Sulfanilamide should be the drug of choice in septic abortion. Anoxemia can be effectively combated with methylene blue.

Acknowledgments

I wish to thank the Maternal Mortality Committee of The Philadelphia County Medical Society for the privilege of having access to the records for the past ten years, and I wish especially to express my thanks to Miss Dorothy Malkiel, Statistician for the Philadelphia County Medical Society, whose untiring help made this study possible.

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Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

A METHOD FOR CATALOGUING DATA FROM RECORDS OF MATERNAL DEATH

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BROOKLYN, N. Y.

*(From the Committee on Maternal Welfare of the Medical Society of the
County of Kings)*

THROUGHOUT the United States, committees engaged in critical analysis of local experience have been accumulating case records which contain valuable information as to the actual causes of maternal death. The worth of these records grows with the years. Of obvious value for statistical comparisons, their content may be made the source of material for closer examination and perhaps publication.

The Committee on Maternal Welfare of the Medical Society of the County of Kings has in its files several hundred records in which the controllable factors in maternal death have been well developed, without identification of patient, physician or hospital. It is important to keep an accurate record of the results of committee discussions, yet it is unwise to record this information in the form of detailed minutes. Legal inquiry into the physician's responsibility for death may bring about unpleasant situations.

We have devised a very satisfactory method for the continuous compilation of data by attaching to each case record two multigraphed sheets as shown in Table I and Table II. One entitled "Data on Case History" contains all the historical data worthy of note. The other shows the primary and secondary causes of death, as agreed upon by the committee, as well as the controllable factors concerned. Both these sheets are checked, during or directly after a meeting of the committee, and the causes of death, which need not coincide with official coding, are written.

Later, each item is posted on its own proper card, which will be found in one of three files marked "Historical Data, Controllable Factors or Causes of Death"; the notation includes three numbers, the first two identifying the case and the hospital where death occurred, and the third the principal cause of death assigned (Table III). The following case will illustrate this:

A white primipara was admitted to the hospital in active labor at term. Her prenatal course was good. After 12 hours the cervix was fully dilated, the vertex was found in L.O.A. position, and within an hour the caput could be seen. Under gas-oxygen-ether anesthesia, episiotomy was performed, and a 7-pound living fetus was delivered by forceps. Ten minutes later bleeding occurred. Unsuccessful efforts to express the placenta were followed by more profuse bleeding. A consultant thereupon packed the uterus with the placenta in situ. Hemorrhage continued for two hours, and the patient's condition becoming progressively worse, she was given an infusion of 1,000 c.c. of 5 per cent glucose. The uterine pack was then removed and the placenta expressed quickly by Crédé. Profuse hemorrhage followed and she died 20 minutes later. Various cardiorespiratory stimulants had been given prior to death.

TABLE I. DATA ON CASE HISTORY

Primipara	White	Puerperal death
Multipara	Colored	Nonpuerperal death
Home delivery	Illegitimate	Poor prenatal care
Home death	Midwife delivery	Post-mortem delivery
Ambulance delivery	Midwife care	Undelivered
Ablatio placentae	Contracted pelvis	Missed abortion
Abortion	Diabetes	Mole
Acute nephritis	Eclampsia	Obesity
Acute yellow atrophy	Ectopic	Pelvic tumor
Anemia	Essential hypertension	Poliomyelitis
Appendicitis	Fibroid	Postmaturity
Bronchopneumonia	Hydramnios	Previa
Carcinoma	Hydrocephalus	Prolapsed cord
Cardiac	Hyperemesis	Psychosis
Cerebral hemorrhage	Influenza	Pyelonephritis
Cervical scar	Large fetus	Syphilis
Cholecystitis	Lobar pneumonia	Tuberculosis
Chorioepithelioma	Long labor	Thyroid
Chronic nephritis	Miscellaneous*	Toxemia
Contagious disease		
(Previous operation)	Fixation uterus	Previous x-ray
Amputation of cervix	Myomectomy	Vaginal plastic
Cesarean section		
Occiput posterior	Breech	Face
Transverse presentation	Multiple pregnancy	Precipitate labor
Artificial rupture of membranes	Hysterotomy	Posterior position
Bag	Induction of labor	Postmortem section
Breech extraction	Manual dilatation of cervix	Spinal anesthesia
Cesarean	Manual removal placenta	Spontaneous delivery
Dilatation and curettage	Mutilating operation	Sterilization
Dührssen forceps	Myomectomy	Uterine pack
Forceps	Porro	Vaginal pack
		Version
Anuria	Laceration cervix	Sepsis, nonoperative
Dilated stomach	Laceration vagina	Sepsis, operative
Embolism	Paralytic ileus	Shock, nonoperative
Gas bacillus infection	Peritonitis	Shock, operative
Hemorrhage	Phlebitis	Separated symphysis
Inversion uterus	Rupture of uterus—probable	Transfusion reaction
Intestinal obstruction	Rupture of uterus—proved	Upper respiration infection
Stillbirth	Neonatal death	Autopsy

*Checked for any unusual complication or associated disease and the complication or disease written beneath and on the file card marked "Miscellaneous."

The committee assigned this death to post-partum hemorrhage. It was agreed that manual removal of the placenta should have been carried out, and that blood transfusion, not intravenous glucose solution or cardiorespiratory stimulants, should have been given. Table I was therefore checked for primipara, white, puerperal death, forceps, uterine pack and hemorrhage. Table II was checked for intravenous fluid, packing, retained whole placenta and transfusion, after post-partum hemorrhage was written as the primary cause of death.

All our cases have been catalogued in this way, so that it is now possible to review any subject. If, for example, we wish to know the part played by inadequate or no transfusion in our mortality statistics, the transfusion card in the controllable factors file would tell us the total number of cases, principal causes of death, and the num-

TABLE II. CAUSES OF DEATH

PRIMARY -----	
SECONDARY -----	

CONTROLLABLE FACTORS	
Abortion, induced	Long labor
Abortion, self-induced	Midwife
Abortion, therapeutic	Operation, choice of
Abortion, unknown	Operation, time of
Accouchement forc�	Packing
Analgesia	Patient
Anesthesia	Pituitrin
Asepsis	Placenta, retained part
Bag induction	Placenta, retained whole
Bougie induction	Pregnancy
Breech extraction	Prenatal care
Cervix	Previous surgery
Cesarean section	Rupture membranes
Diagnosis	Shock therapy
Episiotomy	Syphilis
Forceps	Traction on cord
Hospitalization	Transfusion
Incidental surgery	Treatment
Intravenous fluid	Version
Large fetus	

TABLE III. PLACENTA PREVIA

*C 52—34—149 ¹	-----	-----
D 13—22—148 ³	-----	-----
etc.		

*Note that each case is indicated by three notations. The first, C 52, represents the individual case and in our system the letter "C" stands for the year 1939. The second number, 34, is the hospital. The third, 149¹ is the principal cause of death.

ber of cases annually, since each identifying number includes a letter which indicates the year. Case records may then be withdrawn from the files for detailed information. In the same way, the frequency of prenatal complications associated diseases, operative procedures, or any other factor in which the obstetrician may be interested may be quickly discovered. Yearly summaries and comparisons, which we once found difficult and time consuming can now be prepared with ease.

1313 BEDFORD AVENUE

Society Transactions

PHILADELPHIA OBSTETRICAL SOCIETY

MEETING OF MAY 6, 1943

The following papers were presented:

- A Survey of Abortion Deaths in Philadelphia From 1931 to 1940 Inclusive. Henry J. Sangmeister, M.D. (For original article, see page 755.)
- Further Observations on the Use of Low-Dosage Irradiation in Dysfunctional Menstrual Disorders. Charles Mazer, M.D., and Rose Greenberg, M.D. (by invitation). (For original article, see page 648.)
- Constitutional Inadequacy in Women: Gynecological Aspect. Edward A. Schumann, M.D.
-

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF APRIL 16, 1943

Case Report:

- Full-Term Abdominal Pregnancy. Alfred J. Kobak, M.D. (Published in the October issue, page 577.)

The following paper was presented:

- Carcinoma of the Cervix. Consideration of Certain Factors Pertaining to Its Control. Norman F. Miller, M.D., Ann Arbor, Mich. (For original article, see page 625.)
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Erratum

In title of the article, "The Effect of Complementing the Diet in Pregnancy With Calcium, Phosphorus, Iron, and Vitamins A and D," by Fred L. Adair, M.D., William J. Dieckmann, M.D., Herbert Michel, M.D., Florence Dunkle, M.S., Sylvia Kramer, Ph.D., and Edna Lorang, B.S., Chicago, Ill., which appeared in the July issue, page 116, should have read:

*"The Calcium, Phosphorus, Iron and Nitrogen Balance
in Pregnant Women."*

Department of Reviews and Abstracts

Selected Abstracts

Analgesia and Anesthesia

Rucker, Edwin: Intravenous Anesthesia in Obstetrics, Virginia M. Monthly 70: 35, 1943.

Sodium pentothal has been used by the author in 100 obstetric patients. No attempt was made to select the cases for intravenous anesthesia though at first it was given timidly to patients who had received heavy sedation during labor. This is now thought to be of no importance. Fetal apnea was encountered rarely. Using a 2.5 per cent solution of sodium pentothal, the average dose was 625 mg. The greatest dose was 1,500 mg. and the smallest 75 mg. The drug was administered after full dilatation of the cervix and the patient then prepared for delivery. A perineal nerve block with 1 per cent procaine was done and the intravenous injection was discontinued as the head was being delivered.

For dilatation and curettage sodium pentothal was used following atropine hypodermically and in cesarean section it was administered just before opening the uterus and continued until the uterine incision was closed, the rest of the operation being performed under local procaine infiltration. It is advisable to administer oxygen constantly and the patient's airway must be maintained. Two fetal deaths occurred in this group, the first a four and one-quarter pound twin from a toxic mother. The second fetus was dead on admission to the hospital. There was no maternal mortality.

WILLIAM BICKERS

Figueiredo, Ivan deOliveira, and Centola, Amadeu Ludovico: Intrapartum Perineal Anesthesia in Primiparas, Rev. méd. munic. (Rio de Janeiro) 3: 509, 1942.

De Oliveira Figueiredo and Ludovico Centola carried out perineal anesthetics during the expulsive stage in a series of 117 primiparas. The technique used was based on DeLee's method of infiltration of the perineum for episiotomy.

The results obtained in the present series indicate that perineal infiltration, although not abolishing completely the pain produced by distention of the vagina, vulva and perineum during the expulsive stage, diminishes it materially. It also facilitates the common measures for protection of the perineum against laceration. If episiotomy becomes necessary, it can be performed easily, although in a great number of cases the authors achieved perineal relaxation they do not claim success in all cases. Among the present series were 17 elderly primiparas with four lacerations, an incidence of 23.5 per cent. In a comparable series of nonanesthetized elderly primiparas the percentage of perineal lacerations was 44.4 per cent. The average duration of labor following anesthesia was 27 minutes in both the young

and elderly primiparas. The method was used in two cases of breech delivery without a perineal tear; in 11 cases of low forceps delivery with success in nine, and in one case of embryotomy, likewise with success. The total incidence of perineal lacerations among the 117 cases was 17.3 per cent as compared with 49 per cent in a series of 100 nonanesthetized primiparas. The use of perineal infiltration anesthesia is recommended in primiparas, multiparas with intact perineum, in cases of eclampsia, in women who exhibit fear and in cases of breech presentation.

J. P. GREENHILL

Calvo, J. A.: Fifteen Hundred Fifty Cases of Obstetric Anesthesia With Intravenous Evipan Sodium, Arch. Clin. Obst. y Ginec. Eliseo Cantón 1: 291, 1942.

J. A. Calvo finds that the use of this anesthetic during labor is harmless for the woman when there are no contraindications. The technique is simple and requires no expensive or complicated apparatus and there is no danger of explosion. It hardly influences the uterine contractions, sometimes increasing the interval between them; it does not oppose the action of posterior pituitary lobe extracts. Of all the drugs used to obtain painless labor, evipan sodium has probably the lowest deleterious action on the fetus; it is practically harmless when used intravenously and in fractionated doses. The toxic doses are far removed from the anesthetic doses, and the extremely rapid elimination of evipan makes it an indirectly controllable anesthetic. By following an appropriate technique and associating it with sedatives during the period of dilatation, painless labor can be obtained during expulsion in 98 per cent of the cases, whether primiparas or multiparas. The method should be used only in clinics and hospitals, so that it may be controlled by a competent and experienced personnel. The drug does not cause any late complications in mother or child. It produces sleep and amnesia in an agreeable manner. Waking is rapid and is not followed by vomiting or any ill feeling. Its cost is relatively low; it can be kept indefinitely. Compared with all the other drugs used to relieve pain during labor and expulsion, it is the least toxic and the easiest to administer.

J. P. GREENHILL

Leon, Juan: Obstetrical Analgesia: Barbiturate Twilight Sleep in Labor, With Special Study of Sodium Pentobarbital, Arch. Clin. Obst. y Ginec. Eliseo Cantón 1: 101, 1942.

Juan Leon states that sodium pentobarbital alone or in combination is not the ideal analgesic, as it fails in 22.8 per cent of the cases unless dangerously high doses are used. It acts much better as an amnesic than as an analgesic. Its soporific power is high: it produces deep sleep in 80 and somnolence in 20 per cent of the cases, but causes strong excitement in 6.7 and slight excitement in 25.2 per cent. Temporary vomiting occurred in 10.9 per cent. Careful observation of the uterine dynamics showed that in most cases the drug has no pernicious influence on labor. The progress of dilatation is decreased in 2.3 per cent, but is accelerated in 72.9 per cent. Suppression of cervical spasm is the greatest advantage offered by the barbiturates. The expulsive stage is of normal length in primiparas and multiparas, and the number of interventions is decreased. The frequency of perineal lacerations (24.7 per cent) is due to the difficulty of protecting the perineum in agitated women. Placental delivery is undisturbed. Despite infractions of the rules of asepsis which inevitably occur with agitated patients, puerperal infection is rare, but unfortunately respiratory complications are not exceptional. There was no maternal mortality, while the noncorrected stillbirths amounted to 0.47 per cent and the corrected percentage was zero.

The advantages of sodium pentobarbital and its combinations are relative simplicity of the method, low cost, high percentage of amnesia, practically absolute harmlessness for the mother, absence of disturbances of labor, less influence on the child than with other drugs. Its disadvantages are impossibility of stopping its effects, low analgesic power, excitement of the patient and numerous personnel required so that the method can only be used in specially organized clinics.

J. P. GREENHILL

Malignancies

Kamniker, Hellmut: Genital Carcinoma in Young Women, *Wien. Med. Wchnschr.* 89: 415, 1939.

The author reviews a total of 2,277 cases of genital carcinoma which had been seen at the University Woman's Clinic in Vienna between the years 1921 and 1933. All of the patients had been observed carefully and the survivals followed for at least 5 years. The author's series is first broken into 1,744 primary cases of carcinoma of the genital tract and 523 cases of recurrent carcinoma. He proceeds then to discuss the results observed from treatment of carcinoma among the younger age group, of 30 years or less and compares this series with the patients in a second series, aged 31 to 35 years.

Among 1,199 cases of carcinoma of the cervix there were 42 patients, 20 to 30 years of age, 3 of this group were between 20 to 25 years of age, and 18 cases were pronounced cured and without evidence of metastases after 5 years, an absolute cure of 45 per cent. There were 80 women having carcinoma of the cervix in the 31- to 35-year age group and 32 of these patients were pronounced cured after a 5-year follow-up, hence 50 cures from among 122 cases, 41 per cent, between the ages 20 to 35 years.

The 1,199 cases of carcinoma of the cervix were graded clinically, viz.: 631 cases, 53 per cent, Groups I and II; 568 cases, 47 per cent, Groups III and IV. Kamniker states that but 12 of the 42 cases, aged 30 years or less, were included among the clinical Groups III and IV, while 30 cases, 71 per cent, fell into the clinical Groups I and II. In the total series there were 72 per cent 5-year cures among Group I; 43 per cent among Group II and 15 per cent among Group III in contrast to the younger aged group which revealed 73 per cent, 5-year cures, among Group I; 42 per cent, among the Group II and 22 per cent among Group III. Twenty-nine of the younger group underwent radical panhysterectomy (Schauta's Operation), and 20 of these patients survived 5 years or longer; one case remained permanently cured with but a cervical amputation (a Group I case), while the remaining 13 cases were treated with radiation therapy with but a single case reaching a "permanent cure."

There were 115 cases of fundal and 63 cases of vaginal carcinoma. Among these two groups there were no patients below 30 years of age. There were 157 cases of ovarian neoplasm among which were 2 cases under 20 years of age; 3 between 21 to 25 years and 5 cases between the ages of 26 to 30 years. Among these 10 younger women two were pronounced "permanently cured."

The author concludes that carcinoma in the younger person is no more malignant than carcinoma among the older. He states that radical surgery should not be withheld because of a patient's youth and that it is, . . . "better to have a living female with a very short vagina than a dead patient." The permanent cures are much better in the younger aged group, 45 per cent, in contrast to 17 per cent 5-year survival among his series of 156 cases over the age of 60 years, for the latter present poorer operative risks and are subject to a greater incidence of intercurrent infection.

CLAIRE E. FOLSOME

Pearson, Bjarne, M.D., and Garcia, Manuel, M.D.: Spread and Metastasis in Carcinoma of the Cervix Uteri, *New Orleans M. & S. J.* 95: 215, 1942.

A study of 74 cases of carcinoma of the cervix coming to autopsy has been reported with the purpose of observing carefully the routes of spread in order that a more accurate and effective method of irradiation might be found. In 32.7 per cent there was extension to the vagina; in this group there was extension along the recto-vaginal septum in 17.3 per cent and the vesicovaginal septum in 8.6 per cent. There was ureteral constriction with hydronephrosis in 65 per cent of the cases and this is described as the most common cause of death; uremia being the terminal event. Intestinal obstruction occurred in 12.1 per cent and was the cause of death in 6.7 per cent. Distant metastases were present in 25.7 per cent of the cases and were found most commonly in the liver, lung, pleura, and peritoneum. It is pointed out that local spread occurs predominantly in the lateral direction, but that spread in the sagittal planes, anteriorly and posteriorly, is frequent and presents methods of irradiation which are not effective in their prevention.

WILLIAM BICKERS

Buess, H.: A Case of Perforation of a Carcinomatous Malformed Uterus, *Monatschr. f. Geburtsh. u. Gynäk.* 113: 260, 1942.

The author describes a case of a double uterus in which an adenocarcinoma was present in one horn. Perforation took place in the involved horn.

J. P. GREENHILL

Simeon T. Cantril, M.D., and Franz Buschke, M.D.: Carcinoma of the Cervical Stump, *Western J. Surg.* 50: 454, 1942.

Carcinoma of the cervical stump made up 6 per cent of the total cervical carcinomas seen by the authors. Approximately 1 per cent of all cervixes left after subtotal hysterectomy developed carcinoma. The patients with stump carcinoma are seen earlier than those with other cervical malignancy and approximately 50 per cent are stage I and II. This is the reverse of the distribution of carcinoma of the cervix uncomplicated by previous subtotal hysterectomy. The treatment of the stump lesion is more difficult and hazardous to the patient. Radium can rarely be placed in the cervical canal because of shortening and one must rely upon proper distribution of the radium tandem in the vaginal vault plus deep x-ray treatment. The author employed a minimum of 4,000 mg. hours plus 10,000 roentgens through six portals. The incidence of proctitis and cystitis is therefore much higher following this treatment of stump carcinoma. In one case with a cauliflower growth, the treatment was intravaginal roentgentherapy followed by radium.

The subtotal versus the total hysterectomy is considered and the author feels that subtotal hysterectomy is a justifiable procedure only after cervical malignancy has been ruled out by careful examination of the cervix and biopsy of the endocervix. In all chronic lacerated cervixes the procedure of choice is total hysterectomy. Attention is called to the fact that one-third of cervical carcinomas begin high in the endocervix not visible by speculum examination.

WILLIAM BICKERS

Simpson, Burton T., M.D., Thibaudau, Alphonse A., M.D., and Burke, Eugene M., B.S.: Adenocarcinoma of the Cervix, *New York State J. Med.* 42: 767, 1942.

The authors present a study of 63 examples of adenocarcinoma of the cervix treated at the New York State Institute for Malignant Disease. In their series the age incidence was found to approach more nearly the age incidence of carcinoma of the body of the uterus, 34 per cent of the patients being over 60 years of age, 31 per cent of these women were nulliparas. Treatment was by radiation therapy.

In considering the prognosis, due attention must be given to both the histologic grade of malignancy, as well as to the clinical extent of the disease. The best results were obtained in Grades I or II in which the lesion was limited to the cervix. Forty-six per cent of the patients in this classification were living and well after five years. In the entire series there were 38 per cent of five-year cures.

One case of mucoid adenocarcinoma of the cervix is included which has remained well for 14 years following therapy.

KARL M. WILSON

Gynecological Operations

Leon, Juan: *Histologic Changes Produced in the Genital and Other Organs by Electrotomy*, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 198, 1942.

Histologic changes produced in the genital and other organs by electrotomy with Hyam's conization electrode were studied experimentally by Leon. One rabbit and two dogs were used in these studies. The pathologic changes in the uterus varied according to the tissue obtained by conization. The most prominent changes in the myometrium were tumefaction, homogenization and definite tendency to basophilia of the collagenous substance, whereas the smooth muscle fibers suffered mere stretching of their bodies and nuclei, their staining properties remaining unchanged. These lesions disappeared rather abruptly with the margins of the thin scar produced by conization. The walls of the arterioles included in the peripheral zone of coagulation showed alterations ranging from mere stretching of the muscle fibers to complete homogenization of the entire wall into one amorphous basophilic mass. The glandular and epithelial elements of the mucosa, on the other hand, were affected to a much greater extent than the connective and muscular tissue in the myometrium for the alterations were observed in areas subjacent to the zone of coagulation. The most outstanding feature was elongation of epithelial cells and their nuclei in a direction parallel to that of the electric current. In extreme cases the nuclei appeared as elongated rods in palisade-like arrangement. Similar connective tissue and epithelial changes as in the uterus were observed in the vagina, bladder, kidney, breast, liver, striated muscle, etc., the only variable factor being the peculiarity of the local epithelium. In general, the zone of coagulation did not surpass the extent of 600 to 800 microns, in thickness. This almost lineal line of destruction no doubt assures primary union of the wound margins. However, contrary to the contention of others, Leon believes that the epithelial changes are irreversible.

J. P. GREENHILL

Bazan, Julio, and Althabe, Omar: *The Fothergill Operation in the Treatment of Genital Prolapse*, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 268, 1942.

The Fothergill operation in the treatment of genital prolapse is discussed by Bazan and Althabe on the basis of 354 observations. This method affords the possibility of correcting utero vaginal prolapses and the accompanying retroversion of the uterus by means of an ingenious and simple plastic repair, carried out entirely by the extraperitoneal approach. It is this feature that renders the method safe even in the hands of a novice. Another asset of the operation is that it can be employed in women of any age, except in very old women with total prolapse, in whom the method of Neugebauer-LeFort is the method of choice. The age of the patients in the present series ranged from 25 to 60. The Fothergill method has its special indications in young women in the reproductive age, with a prolapse requiring surgical intervention. In such cases the problem is solved by varying the size of the vaginal flaps and the extent of the colpoperineorrhaphy. In cases of true hypertrophy or elongation of the cervix, especially when hysterometry shows an excess of 8 cm., with the uterus of normal size, amputation of the cervix is the rule, particularly in the presence of cervicitis.

In the series of 354 patients in which this operation was performed the mortality was nil, and the immediate results very good, with exception of an occasional case, in whom amputation of the cervix was carried out because of profuse hemorrhage. Only 94 of these patients could be followed up. The period of observation ranged from ten months to five years. In 87 or 92.55 per cent of these cases, the results were excellent as regards clinical improvement and absence of recurrence. From the viewpoint of future pregnancies, the Fothergill operation is superior to other methods. Of eight women who became subsequently pregnant, seven delivered spontaneously, and in one prophylactic forceps were applied because of pulmonary tuberculosis.

J. P. GREENHILL

Rutherford, Robert M., M. D.: Presacral Neurectomy, *Western J. of Surg.* 50: 597, 1942.

A brief history of presacral nerve resection is presented. Emphasis is placed upon the fact that the operation relieves only that pain originating in the uterus, bladder and upper portion of the vagina. The operation is of no value for pain of ovarian or somatic origin. Anatomy of the plexus is described. Since the operation has been recommended primarily for the relief of dysmenorrhea, it is well to keep in mind that the plexus is made up of sensory afferent fibers as well as motor efferent fibers and it is upon the removal of the sensory fibers that the success of the operation depends. Also, interruption of the sympathetic nerve impulses probably brings about dilatation of the vascular supply of the uterus. Since primary dysmenorrhea is thought to be the result of muscular contractions in the presence of ischemia, the dilatation of the vascular system also contributes to pain relief.

The technique of the operation is described in detail and the end results obtained by the author as well as the experience of other investigators are reviewed. Twenty-three cases done by the author's technique gave 100 per cent relief to thirteen cases; 75 per cent to six cases and 50 per cent relief to four cases. Eight of the patients were followed through a pregnancy with no complication which could be attributed to the operation. No change in libido, menstrual flow, bladder or bowel function was observed in these patients.

WILLIAM BICKERS

Solomons, Bethel, M. D.: Abdominal Hysterectomy, *Irish. J. M. Sc.* 198: 197, 1942.

Dr. Solomons presents a brief review of 790 total and subtotal abdominal hysterectomies done for the most part by himself. The author feels that too many hysterectomies are done, and that this operation should only be performed at or near the menopause. The main indication for operation seems to be hemorrhage, but in cases having myoma he leans to myomectomy rather than the more radical procedure. In discussion of the old question of total versus subtotal hysterectomy, the author takes the same view of advocating the total operation if disease of the cervix is present. A routine follow-up questionnaire was employed, but inasmuch as only 63 per cent of the patients replied, the author feels that little can be gained from this data. It is certain, in view of the poor follow-up, the avowal of never had an instance of carcinoma of the stump is of little significance. There were 17 deaths in the series, giving an incidence of 2.16 per cent. There was no significant difference in the mortality rate for total and subtotal hysterectomy. There were 2 deaths from embolism, and the statement is made that the use of silk may prevent this accident. A large proportion of the deaths was from shock, and inasmuch as there were no deaths after 1937, one guesses that transfusion has probably been more frequently resorted to.

L. M. HELLMAN

Curtis, Arthur H., M.D., F.A.C.S., Barry, J. Aaron, Ph.D., Ashley, Franklin L., M.D., and Jones, Tom, B.F.A.: *The Blood Vessels of the Female Pelvis in Relation to Gynecologic Surgery*, Surg., Gynec. & Obst. 75: 421, 1942.

A continuation of a previous study of the anatomy of the female pelvis and peritoneum is herein presented. There are six full-page color plates showing the distribution of injected pelvic vessels. These represent accurate pictures of dissections carried out in planned serial order. The blood vessels, when portrayed in situ, are shown to be arranged in three groups: the vesical, the uterovaginal, and the hemorrhoidal vessels. The point is also made that the so-called ligaments are made up, to a large extent, of arteries and veins.

L. M. HELLMAN

Martzloff, Karl H., M.D.: *Routine Abdominal Panhysterectomy, as Prophylaxis Against Cancer of Cervical Stump*, Surg., Gynec. & Obst. 75: 628, 1942.

The author takes a conservative stand on the controversial problem of routine panhysterectomy as a prophylactic measure against cancer of the residual cervical stump. A review is given of some of the soundest literature on the subject. The high incidence of stump carcinoma reported by earlier writers is due, in the author's opinion, to cancer already existent at the time of the supravaginal hysterectomy. If three years are allowed to elapse before cases are considered as developing carcinoma in the residual cervix, then the incidence of this type of cancer after subtotal hysterectomy is less than 1 per cent. Total hysterectomy as a routine procedure, except in the hands of well-qualified individuals, has a mortality definitely greater than that encountered in the simple operation. The author does not condemn the procedure when it is undertaken electively by a competent operator on good indication.

L. M. HELLMAN

Bolla, Isidro, M.D., and Bettinotti, Alberto E., M.D.: *Contribution to the Surgical Treatment of Stenosis of the Uterine Cervix*, An. Inst. de May. y Asist. Soc. 2: 110, 1940.

Isidro Bolla and Alberto E. Bettinotti discuss the evolution of the ideas concerning cervical stenosis in dysmenorrhea and sterility during the last decades and consider the existence of congenital cervical stenosis which justifies surgical treatment.

In their own technique, they make bilateral incisions with straight scissors, sectioning more on the inside than the outside so as to get as near as possible to the internal orifice. They keep the two lips of the incision open by interposing two perforated glass balls, 1 cm. in diameter, kept in place by a horsehair suture which is passed through the tissues and the ball. They call attention to the simplicity and practical advantages of this method and the complete absence of any trouble or complication.

J. P. GREENHILL

Peon, Alberto Rendon, M.D.: *Suspension of Uterine Stump by the Round Ligaments in Subtotal Hysterectomies*, Rev. de Cir. de Buenos Aires 14: 155, 1942.

Alberto Rendon Peon noted that in many of his first cases of subtotal hysterectomy the uterine stump descended despite the perfect condition of the perineum. This resulted in bladder disturbances, a feeling of vaginal fullness and even lumbar pain, especially in patients who exerted themselves. Since then, he has systematically made the round ligaments contribute to the suspension of the stump. Notwithstanding their thinness (5 to 6 mm. diameter), these ligaments will resist a traction of 500 to 600 Gm., without rupturing. After resection of the uterus and ligation of the ovarian and uterine pedicles, he excises a cone of tissue from the cervical stump,

sufficient to leave an anterior and posterior flexible wall; he detaches the serous covering from these walls and passes through them a No. 2 chromic catgut suture; he adjusts the free extremities of the round ligaments into the concavity of the stump and insures their fixation and hemostasis by tying the catgut. For additional security, when closing the stump he passes the first right and left sutures through the round ligaments. Careful peritonization follows. In this manner, the stump is suspended by six ligaments: three on each side, or four anteroposterior and two antelateroposterior.

J. P. GREENHILL

Gallucci, José: Stenosis of Uterine Cervix, *Rev. de gynec. e d'obst.* 36: 261, 1942.

José Gallucci states that cervical stenosis is not rare. He has observed four cases. It may be congenital or acquired; the latter is due to many causes, especially to treatment of cervicitis. The clinical forms include adhesion of the canal or the orifices, stricture and agglutination of the orifices by juxtaposition of the cervical mucosa or organization of the normal mucous plug of the cervix. In the anamnesis, previous treatments for cervical discharge must always be inquired into. When a hard, nonelastic and nondilatable cervix is found during labor, it is generally the result of previous electrocoagulation or surgery; sometimes there is no external orifice. In gynecologic cases, there may be sterility associated with amenorrhea; obstructive dysmenorrhea which improves with dilatations; purulent discharge without apparent cause, especially in menopausal women; primary amenorrhea in congenital stenosis, and secondary amenorrhea in acquired stenosis; collection of blood in the cervix, uterus, tubes and peritoneum, but mostly only in the uterus.

If the stenosis is discovered during labor, the cervix is incised and delivery completed by an appropriate obstetrical maneuver. If it is diagnosed at another time, dilatation with Hegar dilators may be considered and should always be used after treatment of cervicitis; amputation of the cervix, using Sturmdorf's method, may be performed in young women, or hysterectomy in menopausal patients.

Of the author's three personal cases, two were the result of radium applications for cervical cancer and one was due to traumatism of labor: As this woman was 41, high amputation of the cervix was performed. The fourth case, seen in another clinic, was discovered during premature labor in a woman who had been treated for cervicitis; incision of the cervix and forceps application solved the difficulty.

J. P. GREENHILL

Stajano, Carlos, and Schaffner, Eduardo: Bilateral Oophorectomy in Trophic Neurosis of Vulva, *Bol. Soc. de obst. y ginec. de Buenos Aires* 21: 183, 1942.

Carlos Stajano and Eduardo Schaffner state that most neurotrophic disorders of the vulva, such as essential pruritus, recurrent chronic eczema, leukoplakia, kraurosis, etc., appear about and after the menopause. For years, the authors tried unsuccessfully to cure these disorders with ovarian extracts, especially estrogen. Then they discovered accidentally the noxious action of senile ovaries when they saw rebellious vulvar lesions undergo favorable changes after castration of old women for uterine lesions. Essential pruritus that has been present for years disappears immediately after the operation. Leukoplakia, associated or not with pruritus, regresses and the vulva may assume a normal aspect in a few weeks.

Many patients were between 60 and 75; they had atrophic and sclerosed ovaries, the removal of which cured pruritus always and leukoplakia frequently. The authors confirm their former concept that the ovary produces morphogenetic hormones, and they add to the syndromes of ovarian hyperfunction and insufficiency that of dysfunction under the term of "toxic ovary."

J. P. GREENHILL

Correspondence

Relaxation of Bandl's Contraction Ring With Adrenalin Chloride

To the Editor:

Since Rucker's Communication in the *Southern Medical Journal* (18: 412, 1925) the fact that adrenalin relaxes constriction rings has been quite widely held. However, the opponents to such belief maintain that the clinical effects noted after administering adrenalin hypodermically have been due to deepening of the anesthesia at the time. Even as recently as the April, 1943, issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, Brown and Wilder make such a statement. So far as I know, no observations have been made of the patient under spinal anesthesia which is uniform in its effect, and therefore, not open to the objection mentioned. This case, therefore, seems worthy to be reported.

A twenty-three-year-old primigravida whose history was essentially negative was admitted to Park View Hospital after being in active labor for more than twenty-eight hours. The fetal head was not engaged and the cervix was undilated. A cesarean section was decided upon and spinal anesthesia used. When the uterus was exposed both the operator, Dr. N. P. Battle, and I noticed a distinct hourglass contraction of the uterus which had not been relaxed by the anesthesia. The constriction ring was about the baby's neck. Five minims of adrenalin chloride was given hypodermically in the deltoid muscle and within three minutes the ring had completely disappeared.

ROCKY MOUNT, N. C.

JULY 30, 1943.

ADAM T. THORP, M.D.

Item

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 12, 1944 at 2:00 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the Secretary by November 15, 1943.

All candidates are now required to have been out of medical school not less than eight years, and in that time to have completed an approved one year internship and at least three years of approved special formal training, or its equivalent, in the seven years following the intern year. This Board's requirements for internships and special training are similar to those of the American Medical Association since the Board and the A. M. A. are at present cooperating in a survey of acceptable institutions. At the last Board meeting held May, 1943, it was decided to give special credit for certain types of military service. All candidates must be full citizens of the United States or Canada before being eligible for admission to examinations.

All candidates will be required to take the Part I examination, which consists of a written examination and the submission of twenty-five (25) case history abstracts, and the Part II examination (oral-clinical and pathology examination). The Part I examination will be arranged so that the candidate may take it at or near his place of residence, while the Part II examination will be held late in May, 1944, in that city nearest to the largest group of candidates. Time and place of this latter will be announced later.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

PAUL TITUS, M.D.
Secretary.

September 17, 1943.

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Original Communications

THE DEVELOPMENT OF THE PERIURETHRAL GLANDS IN THE HUMAN FEMALE*

JOHN W. HUFFMAN, M.D.,† CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University Medical School and the Gynecological Service of Passavant Memorial Hospital)

IT HAS been known for many years that occasional small glands, homologues of the male prostate, are present about the female urethra. In 1880 clinical interest in these structures was awakened by Alexander Skene's description of two larger ducts lying on each side of the urethra. His name has subsequently become attached to them. The origin of these structures, their relation to the urethra and to each other has been the subject of considerable study. This knowledge should be of interest not only to the histologist and embryologist but to the clinician as well for through it a better appreciation is to be had of the importance of these structures in the pathologic states occurring in and about the female urethra and also in the anterior vaginal wall. The importance of inflammations of Skene's ducts and glands in infections of the female genitalia, particularly those of gonorrheal origin, is common knowledge. The role of the periurethral glands in urethral pathology is less well known.

That these glands of the female urethra were probably rudiments of the prostate was alluded to by Regneri deGraaf in 1672. Astruc in 1737 described "the prostates or rather one prostate which in the female surrounds the urethra and opens with two small mouths into the

*Presented at a meeting of the Chicago Gynecological Society, May 21, 1943.

†Now Lieutenant-Commander, MC-V (S) USNR. Statements contained herein are the writer's and are not to be construed as reflecting the views of the Navy Department.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

vagina just under the clitoris and with several lacunae along the sides of the urethra." Virehow in 1853 found glands along the female urethra. Because of the similarity of the calculi in them to the concretions found in the male prostate he considered them to be homologues of the male gland. Between 1880 and 1890 the question of a female prostate was revived by a group of French authors (Robin and Cadiat, Martin and Leger, and others). They found no gland formations in the region of the bladder and questioned the existence in the female of a homologue of the prostate. Tourniaux, in 1889, pointed out that the urethral glands of the female, together with the para-urethral ducts are homologues of the prostate. This opinion was agreed with by Aschoff, Oberdieck and others who found deep lacunae along the middle third of the urethra which they concluded to be homologous with the prostate. According to Nagel, Waldeyer, and Felix only the para-urethral ducts are prostatic homologues. Koks and others considered the periurethral gland structures to be remnants of wolffian duct origin. Gustav Pallin, in 1901, believed that the glands of the female urethra were not homologous with the whole male prostate but only with that portion of the male gland arising cephalad to the urogenital sinus. Evelyn Wyatt reconstructed a model of the urethra and vagina of a three and one-half months' fetus. The model showed an exuberant growth of glandular tissue from the posterolateral and the anterior wall of the urethra. He felt that there could be no doubt but that the glandular organ surrounding the female urethra was a homologue of the male prostate and that the female urethra is the counterpart of the whole of the prostatic urethra in the male. In 1922, Johnson made wax reconstructions of several female fetal urethras. There were urethras from 60 mm., 75 mm., and a 176 mm., fetus in his series. He also prepared sagittal sections of an 80 mm. fetus and cross sections of the urethra of a 275 mm. fetus and of one adult urethra. He found that in the 275 mm. stage several glands were present just outside the urethral orifice and that they therefore belonged to the urogenital sinus. He states that these glands conform in position to the para-urethral glands of Skene and that their origin as prostatic ducts belonging to the urogenital sinus cannot be doubted.

This paper is an attempt to correlate the findings of those who have previously described the development of the periurethral glands and para-urethral ducts and to amplify those findings in certain particulars, especially as regards the origin of the para-urethral ducts. Additional data will be contributed which are pertinent to the discussion concerning the origin of glandular structures (other than the vestibular glands) from the female urogenital sinus below the müllerian tubercle.

For the purpose of this study serial sections have been prepared from the urethras and external genitalia of female fetuses of 50 mm., 80 mm., and 128 mm. crown-rump length. Serial sections have also been prepared of fetuses of 224 mm. crown-rump length demonstrating the urethra in its entirety and also the ventral two-thirds of the anterior vaginal wall. Serial sections of six adult female urethras demonstrating the detailed anatomy of the periurethral glands and the perinurethral ducts have likewise been utilized in correlating the fetal

findings with counterpart structures in the adult. Wax model reconstructions have been constructed to illustrate certain points discussed.

In the youngest (50 mm.) fetus of this group sex differentiation had already become well established. By this stage the phallus had become the clitoris, the labioscrotal swellings had become the labia majora and the external folds of the urogenital opening formed the labia minora. This urogenital or urethrovaginal opening communicates with the urogenital sinus which, it will be recalled, developed primarily as a result of a division of the cloaca. When the embryo was much younger, approximately 5 cm. in length according to Felix, the cloaca began to undergo division, the dorsal one-third being separated to form the rectum. The ventral two-thirds of the cloaca subsequently divided into two portions, of which the dorsal portion formed the vesicourethral anlage and the pars pelvina of the urogenital sinus while the ventral portion formed the pars phallia of the urogenital sinus. In the female most of the bladder, the lower portion of the urethra, much of the vulva and perhaps part of the vagina develop from the vesicourethral anlage and the pars pelvina, while a small portion of the vestibule ventral to the meatus of the urethra is created from the pars phallia.

During the division of the cloaca the distal ends of the mesonephric ducts opened close together on Müller's tubercle in the dorsal wall of the urethra, and the ureters opened upon the lateral walls of the bladder anlage. The müllerian tubercle was first projected into the median dorsal wall of the urethrovaginal anlage by the earlier entrance of the mesonephric ducts. The distal ends of the müllerian ducts, travelling downward, crossed the mesonephric ducts and were eventually pressed together between the mesonephric ducts so that by gradual fusion they formed the single anlage of the uterus and the major cephalad portion of the vagina. In these early stages no suggestion of prostatic anlagen occur until, according to Lowsley, they are first seen in the male embryo of 50 mm. length as small solid epithelial buds arising both above and below the junction of the urethra with the fused müllerian ducts.

As a result of these migrations and divisions of the urogenital structures, when the female fetus has attained a crown-rump length of 50 mm. the urogenital sinus is observed to be a somewhat funnel-shaped relatively large tube with a ventral opening, the ostium urogenitale. It is still of considerable length, wider at its distal end and broader in its ventrodorsal diameter, with slightly folded sides. The epithelium is thick-walled. In one section the anlage of the major vestibular glands first appear as two solid buds arising from the dorso-lateral walls. At its upper limit the müllerian tubercle marking the junction of the urethra and uterovaginal canal, appears as a pronounced nipple-like projection extending into the upper extremity of the urogenital sinus. At this stage the mesonephric ducts open on the lateral sides of the müllerian tubercle. Centrally placed between the mesonephric ducts and pressed against but not penetrating the müllerian tubercle is the thick-walled uterovaginal anlage. Above the tubercle, entering the urogenital sinus at a slight angle is the rather long urethra. It is a small, thick-walled tube with dense, dark epithelium. It widens into the larger bladder anlage which is lined by a thick almost vesicular epithelium.

At this 50 mm. stage no glandular anlagen (other than those of the major vestibular glands) are to be discovered distal to the müllerian tubercle in the walls of the urogenital sinus in the fetus examined in this study. Diligent search was made for gland buds along the lateral, posterior, and anterior sides of the urogenital sinus in the region of the



Fig. 1.—Photomicrographs of three cross sections of the urethra and contiguous structures of a 50 mm. human female fetus. A, a section slightly above the müllerian tubercle, demonstrates the star-shaped urethra (above) the small thick-walled uterovaginal anlage with its accompanying laterally placed wolffian ducts. The other two sections, at levels cephalad to A, demonstrate one lateral (B) and one ventral and one lateral (C) urethral epithelial buds which are the first anlagen of the periurethral glands. ($\times 65$.)

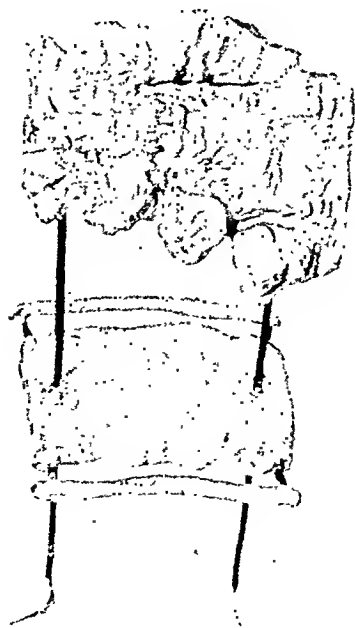


Fig. 2.—Photograph of a wax model reconstruction of a portion of the urethra and uterovaginal anlage of a 50 mm. fetus. Arising from the urethra (above) are two lateral and one ventral epithelial buds which represent the first anlagen of the periurethral glands. The broad flattened uterovaginal anlage below is accompanied by the laterally placed wolffian ducts.

müllerian tubercle and below it; none were found. Above the tubercle, however, in the true urethra four buds, one ventral and three lateral were observed (Fig. 1), which on wax reconstruction are definite epithelial thickenings extending from the urethral wall into the mesenchyme (Fig. 2). These may be considered anlagen of the female prostate. In the 60 mm. fetus Johnson observed "14 epithelial buds belonging to the urethra and 5 to the urogenital sinus." He observed them on the anterior, posterior, and lateral surfaces of the urethra in positions similar to those of the male urethra.

In the 75 mm. fetus Johnson found the urethral glands more numerous (26 buds in all) and that they were present both on the urethra, the urogenital sinus and occasionally on the lower end of the uterovaginal canal. He also observed small tubular glands on the dorsum of the urogenital sinus which corresponded with the small sinus glands of Littre in the male. Johnson prepared midsagittal sections of an 80 mm. embryo which showed a few prostatic glands along the urethra and one at the lower end of the uterovaginal canal. He found no glands belonging to the urogenital sinus in the midsagittal plane but states that a few were found in adjacent sections. In the horizontal transverse sections of the 80 mm. fetus in the present series the decreased cephalopelvic length and the increased dorsoventral widening of the urogenital sinus is well demonstrated. The anlagen of the major vestibular glands are now well marked as branched solid buds arising from the lateral walls of the urogenital sinus. Several small solid buds corresponding to those which Johnson considered to be homologues of the glands of Littre are evident on the dorsal wall of the sinus. No glands or gland buds were observed arising from the upper walls of the urogenital sinus nor from the uterovaginal anlage. The latter is still a solid flattened ribbon-like structure buried in the depths of the thick genital cord. Above the level of the union of the uterovaginal anlage with the urogenital sinus the urethra forms an open tube of considerable size surrounded by a dense wall of mesenchyme. Many epithelial buds may be observed protruding into the mesenchyme about the urethra (Fig. 3). These, with the crypts which enter them from the urethra, are a further stage in the development of the female prostate. As the bladder is approached the epithelial buds disappear. Cephalad the urethra becomes flattened anteroposteriorly while the mesenchymal thickening about it remains heavy.

In the 128 mm. embryo of this series the urogenital sinus is notably less deep than in the previous stages. It now constitutes a deep vestibule, narrow laterally and long dorso-ventrally, at the upper limit of which the urethra opens. The walls of the sinus are elevated in marked folds and the squamous epithelium which lines it is thin and more dense than in earlier stages. Slightly below the entrance of the urethra the major vestibular gland duets branch off from the dorsal lateral walls of the sinus and extend deeply into the mesenchyme where multiple glandular elements appear. These glandular elements are similar in every characteristic to the adult gland.

Buried in the connective tissue dorsal to the urethra and connected to the upper end of the urogenital sinus by a plate of dense tissue is the still solid vaginal anlage. At this stage the lower portion of the vaginal anlage is comprised of two sinovaginal bulbs which later form that part of the vagina immediately above the introitus. Above this point the vagina is at first a markedly folded and serrated solid thin

ribbon of stratified squamous epithelium. Above it becomes a thinner less folded but still solid flattened tube.

The urethra is larger than in the preceding stages. It is a rounded tube flattened dorsoventrally. Its epithelium is cuboidal in type and of but one or two cell layers in thickness. Above the level of the junction with the urogenital sinus there are many periurethral gland buds (Fig. 4). Some of these gland buds retain the solid character seen previously, but others of them have open lumina and there is a beginning tendency for branching to occur (Fig. 5). These glandular anlagen are present in the distal portion of the urethra on the lateral, dorsal, and less commonly on the ventral walls of the urethra; none are present in that part of the urethra nearest the bladder. At this stage the muscle layers about the urethra are well defined with an exceptionally heavy circular muscle coat in the upper one-third of the urethral wall.

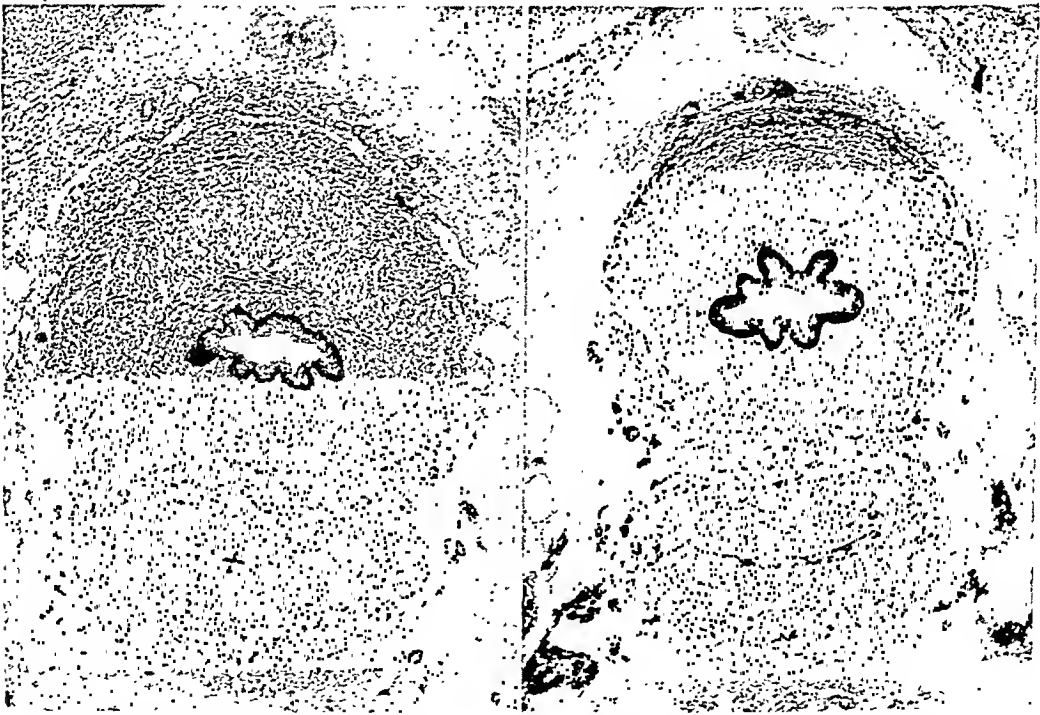


Fig. 3.—Photomicrographs of two cross sections through the urethra (above) and uterovaginal anlage (below) of an 80 mm. human fetus. The solid epithelial buds arising from the urethral mucosa are a further stage in the development of the periurethral glands. (X65.)

No gland or gland anlagen which could be interpreted as precursors of the para-urethral duets could be found opening into the vestibule. No glands or gland anlagen arose from the vaginal epithelium in this fetus.

Serial sections of the urethra of a female fetus of 224 mm. were utilized for the study of the later fetal stages of the development of the periurethral and para-urethral glands. The urethra of its female twin, slightly larger, was sectioned later for comparison. The two were found to agree in all essentials.

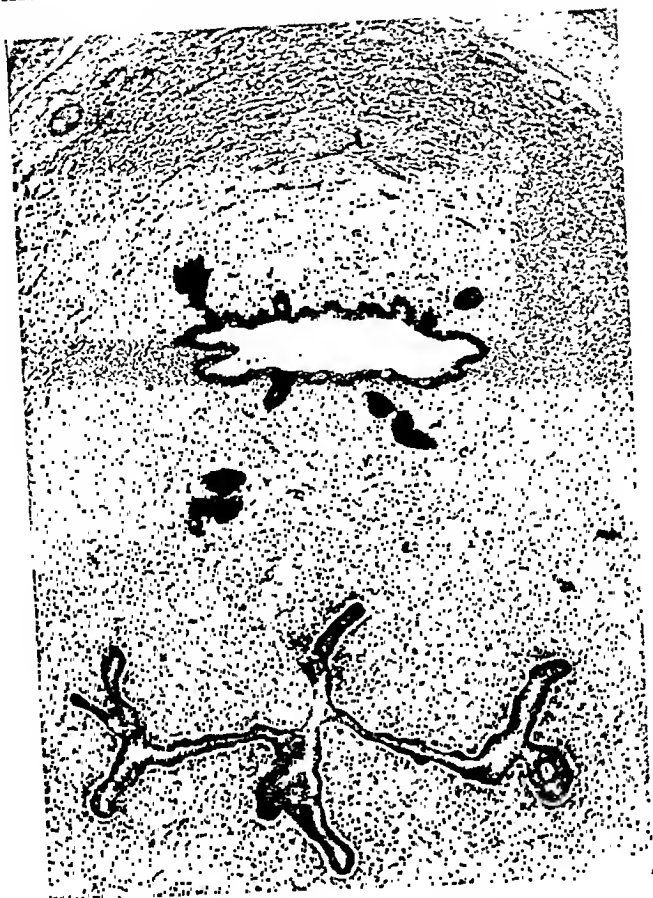


Fig. 4.—Photomicrograph of a cross section through the urethra (above) and vaginal anlage (below) of a 128 mm. human fetus. Periurethral gland buds are evident arising from the urethra and extending into the tissues about it. ($\times 60$.)



Fig. 5.—Photomicrograph of a cross section through the urethra of a 128 mm. human fetus. Some of the periurethral gland buds retain the solid character seen previously, but others have open lumina and there is a beginning tendency for branching to occur. ($\times 60$.)

At this stage the vestibule is a shallow groove. It is all that remains of the urogenital sinus. Deeper sulci are present beside the urethra. In the adult these sulci are depressions which make the meatus open upon a flattened hillock. In the fetus they are quite deep due to the still disproportionately large size of the labia. As a result, cross sections through the transverse plane of the urethra and the upper limits of these sulci give the impression that gland-like processes exist at each side of the urethra (Fig. 6). If, however, wax model reconstructions of this area are prepared and compared with the adult it will be observed that these structures are in reality the sulci beside the urethral meatus as previously mentioned (Fig. 7). They are not to be con-



Fig. 6.—Photomicrograph of a cross section through the urethra and vagina at a level slightly above the meatus of a 224 mm. human fetus. The mucosa of the centrally placed urethra is unusually thick, the lumen small. The vagina (below) is markedly folded, the epithelium thick. Above the corpora cavernosa of the clitoris forms a paired structure. The glandlike processes lateral to the urethra are the upper limits of the sulci formed by the labia minora and majora. ($\times 10$.) (See Fig. 7.)

fused with anlagen of either the periurethral or para-urethral glands. There are no glands to be discovered in the vestibular or vaginal mucosa. The major vestibular glands are large with many branches resembling those in the adult, the ducts opening from the vestibule lateral to the vagina.

There are no glands evident in the most distal portion of the urethra in the 224 mm. specimens studied. The urethral wall immediately



Fig. 7.—Photograph of a wax model reconstruction of a transverse section through the external genitalia of a 224 mm. human female fetus at the level of the meatus. At this stage the vestibule is a shallow groove. Deep sulci at each side of the urethra and vagina are formed by the labia minora and labia majora. The upper portions of these sulci lateral to the urethra are quite deep and may give the impression when seen in single cross section, that they are glandular structures. (See Fig. 6.)



Fig. 8.—Photomicrograph of a transverse section through the upper portion of the lower third of the urethra of a 224 mm. human female fetus. The folded anterior vaginal wall is included in the lower half of the section. The branched periurethral glands are widely disseminated about the urethra in a manner comparable to that of the adult. (See Fig. 9.) (X10.)

within the meatus was unusually thick due to the many layers of stratified squamous epithelium lining it. The lumen is consequently of small size. The glands nearest the meatus arose from the dorsal and lateral walls of the canal. In the same area but slightly above it a ventral dilation of the thickened urethral wall represents what may be a diverticulum. That it is a urethral pocket is evidenced by the fact that it does not branch away from the urethra, it is lined by stratified squamous epithelium and it is devoid of secretory cells. The greatest number of periurethral glands arise from the lateral, ventral

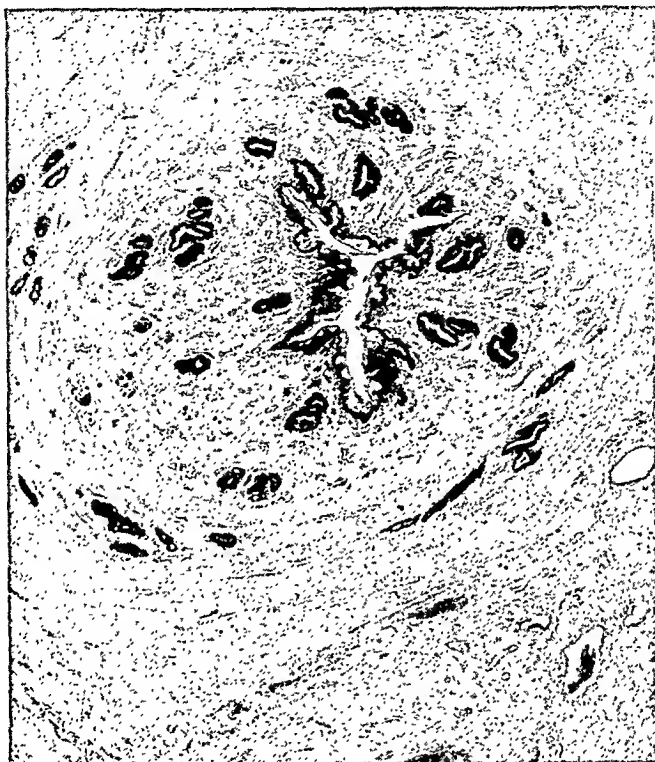


Fig. 9.—Photomicrograph of a transverse section through the urethra and para-urethral structures of an adult human female at a level 1.2 cm. above the meatus. The numerous periurethral glands are evident extending well away from the urethra not only laterally but also dorsally and ventrally. (X24.)

and dorsal walls of the upper portion of the lower third of the urethra (Fig. 8). At this stage they are branched structures extending into the submucosal tissues where they bend cephalad toward the bladder. They are lined for the most part by stratified squamous epithelium with areas of cuboidal epithelium in the more distal portions. The walls are unusually thick and the lumina are disproportionately small.

In the proximal third of the urethra the lumen is large and is flattened laterally, the mucosa is thin and dark and glands are absent.

The serial sections of the six adult urethras examined were made from autopsy material obtained by Dr. Frank Queen.* This material consisted of blocks of tissue containing the external urethral meatus, the anterior vaginal wall and vaginal mucosa beneath the urethra and the urethra and its surrounding connective tissue. In these adult

*Pathologist of Passavant Memorial Hospital, Chicago, Ill.

urethras it was observed that for the most part the glandular structures arose in the distal one or two thirds of the urethra corresponding in this respect to the fetal anlagen. The considerable extent and dissemination of these glandular structures through the submucosal and muscular layers of the urethra was more extensive than had been anticipated (Fig. 9). Multiple orifices of the periurethral glands arise from the mucosa above the meatus. In some instances, on one or both sides of the urethra, two of the periurethral glands assume the large size characteristic of the para-urethral glands described by Skene. The periurethral glands extend not only parallel with the urethra as described by others but they also extend laterally, ventrally and less frequently they also extend dorsally or vaginalward at right angles to the urethra to form widely dispersed glandular nests throughout the muscular walls of the urethra.

Summary

Serial sections have been prepared of the urethras and the lower urogenital area of female fetuses of 50 mm., 80 mm., 128 mm., and 224 mm. crown-rump lengths, and of six adult female urethras. Wax reconstructions of portions of these preparations have been made to illustrate certain points discussed. Anlagen of the periurethral glands were observed for the first time in a 50 mm. fetus. These anlagen appear as four small, solid buds arising from the ventral and lateral surfaces of the urethra above the müllerian tubercle. In the 80 mm. fetus urethral gland anlagen are evident as numerous buds, without branches, developing from the dorsal, ventral and lateral sides of the urethra above the müllerian tubercle. Branched glands are present in the 128 mm. fetus but at this stage, as in the younger embryos, only the area of the urethra above the müllerian tubercle gives rise to them. In the 224 mm. fetus the glandular arrangement is similar to that in the adult. At this stage the lower urethra reveals one diverticular-like pocket but no glandular structures are to be seen arising from the vestibule or the vaginal epithelium. In the adult urethras studied the orifices of all periurethral or para-urethral glands arise from the urethral mucosa. In none of the fetal or adult urethras examined in this series were any glandular structures observed arising from the urogenital sinus below Müller's tubercle, in the vaginal epithelium nor in the vestibule. These observations support Pallin's belief that the female periurethral glands are homologous with only that portion of the male prostate arising cephalad to the urogenital sinus. That this is for the most part true is evident from the material presented herewith. However, the classical work of Wyatt and of Johnson, who found occasional glands arising from the urogenital sinus below the müllerian tubercle make an attempt at correlation of these divergent findings necessary. Several explanations are possible: The most logical would seem to be that occasional small glands in the lower portion of the urethra are carried downward on the lips of the somewhat

trumpet-shaped opening of the urethra into the upper end of the urogenital sinus. As a result, the indistinct union of the urethra and the urogenital sinus makes it appear that these periurethral glands are of sinus origin. It is also possible that occasional small true sinus glands are present in the female but that they are infrequent in number and not present in all individuals. Several small, straight, solid tube-like buds were noted in the 80 mm. fetus arising from the lower walls of the urogenital sinus. These were considered anlagen of Littre's glands which are profuse in the distal male urethra. It would appear from the material studied that the larger para-urethral ducts and glands (Skene's) arise from anlagen above the müllerian tubercle; that they are similar to the other periurethral glands in origin and structure; and, that they, like the periurethral glands, are homologues of that portion of the male prostate which develops above the union of the mesonephric ducts with the urogenital sinus.

Conclusions

1. Anlagen of the periurethral glands are present in a human female fetus of 50 mm. crown-rump length.

2. In the 50 mm., 80 mm., and 128 mm. crown-rump length female fetuses examined in this study the anlagen of the periurethral glands were, in each instance, found only in that portion of the urethra above the müllerian tubercle.

3. It was impossible to differentiate the anlagen of the periurethral glands from those of the para-urethral ducts in any of the fetuses examined.

4. From the material studied herewith it appears that the homologues of the para-urethral (Skene's) ducts are the same as those of the other periurethral glands.

5. No glandular anlagen other than those of several of Littre's glands were discovered in the vestibular mucosa of any of the four fetuses examined.

I wish to express my appreciation to Dr. Arey for affording me the facilities of the Anatomy Department of Northwestern University Medical School where the wax models were constructed.

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Discussion

DR. ARTHUR H. CURTIS.—Additional information on the embryology of the glandular elements of the female urethra is most welcome. In fact, our knowledge of the gross anatomy of the entire perineal region has been entirely inadequate. That in turn has resulted in much confusion and misunderstanding relative to the pathological anatomy and surgical correction of lesions in this region. This is neither the time nor the place for me to do more than emphasize the importance of investigative work in this local field.

DR. HUFFMAN (closing).—What interested me as I constructed the models of the adult urethra and as I examined the patients, was that I could not discover glands of any size arising at any point in the vestibular mucosa beyond the urethral meatus itself; nor have I ever heard any other clinician comment on the presence of these glands, despite the fact that many textbooks describe their presence.

It is my impression that the origin of the urethral glands, when they are present, is at the margin of or just within the urethral meatus: when they arise from the external surface of the labia of the urethral meatus, it is because the latter has become everted due to labor or sexual trauma.

The failure to find glands of any sort in the vestibular mucosa and the absence of para-urethral duct openings in the outer surfaces of the labia of the urethral meatus stimulated me to search in the embryo for glandular structures in the epithelium of the urogenital sinus below the müllerian tubercle. As a result of the study of these comparatively few specimens, I have no reason to change my impression, obtained both from clinical observation and from a study of the serial sections and wax reconstructions, that the periurethral glands arise almost always from the urethra itself. It would appear also that the para-urethral glands and ducts of Skene are more highly developed periurethral glands and that they likewise take their origin from the urethra in a manner similar to the other periurethral glands.

FURTHER EXPERIENCE IN THE MANAGEMENT AND TREATMENT OF CARCINOMA OF THE FUNDUS OF THE UTERUS, WITH FIVE-YEAR END RESULTS IN SEVENTY-FIVE PATIENTS*

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IN 1937, the senior authors presented a detailed report relating to their experience in the management and treatment of carcinoma of the fundus of the uterus. This was based upon the study of 68 patients observed on the gynecologic ward and private services at Jefferson Medical College Hospital, and treated by various members of the staff, between September 1, 1921, and September 1, 1936, with five-year end results in 47 of them. There were no untraced patients in the series.

Since then 59 additional patients have been encountered between September 1, 1936 and September 1, 1942. This provides a total group of 127 patients for further discussion, and for an analysis of the five-year end results in 75 of them. Again, there are no untraced patients (Table I). Variations in management and treatment, with relevant observations relating to the work of others, will be commented upon, and discussed in detail, together with certain conclusions indicated by the survey.

TABLE I. PATIENTS OBSERVED AND FOLLOW-UP

YEARS	NUMBER	TREATED	FOLLOW-UP	PER CENT
1921 to 1937	75	74	75	100
1937 to 1942	52	52	52	100
	127	126	127	100

Age Incidence, Parity, Race

Table II relates to age incidence, parity and race. Most striking are the facts that 79.5 per cent were 50 years of age or older, and 20.5 per cent below this age limit. The latter figure is of special interest when contrasted with our statistics in carcinoma of the cervix which indicate an incidence of 56.6 per cent in patients under fifty. The average age, 56.1 years, is identical with that reported by Masson and Gregg, and similar to that noted by Miller, Healy and others. The incidence of the disease among nulliparous patients is in conformity with that generally reported. The occurrence of fundal carcinoma in Jewish women is definitely higher in our experience than in cervical malignancy (1.2 per cent); the reverse is true among our Negro patients (10.0 per cent). The ratio of patients with fundal carcinoma to those having cervical carcinoma (ward service) agrees with accepted estimates (1:10.8).

*Read at a meeting of the Obstetrical Society of Boston, February 16, 1943.

TABLE II. AGE INCIDENCE, PARITY, RACE

DECADE	PATIENTS	PER CENT
30 to 39	1	.8
40 to 49	25	19.7
50 to 59	54	42.5
60 to 69	45	35.4
70 to 79	2	1.6
Total	127	100.0
Youngest, 37; oldest, 77; Average, 56.1		
Nulliparas, 44; 34.6 per cent (20 unmarried)		
Jewish, 7; 5.5 per cent. Negroes, 4; 3.1 per cent		
Ratio of Carcinoma of Cervix (Ward Service) 1:10.8		

Menopausal Relationship

The patients have been divided into so-called premenopausal and postmenopausal groups.

In the first category are those patients who never experienced a definite cessation of menses, but whose history was one of irregular uterine bleeding without surcease until treatment was instituted (21.3 per cent). The average age of this group was 46.3 years. However, 7 of these patients were 50 years of age or over, and what they regarded as "irregular periods" were evidently intermittent episodes of bleeding of organic and/or functional origin.

The second grouping is made up of those patients who had definitely experienced cessation of menses, and whose irregular bleeding came on anywhere from one to twenty-six years thereafter (78.7 per cent). The average age of these patients was 58.9 years. The average menopausal age of the entire group was 49 years, excluding a group of patients in whom a previous irradiation menopause had been produced. Healy and Brown reported 79 per cent of their patients as postmenopausal, with an average menopausal age of 50 years.

Significance and Duration of Symptoms

All observers agree that irregular uterine bleeding is the most significant symptom of fundal carcinoma. In the above-mentioned premenopausal group, such bleeding occurred as menorrhagia and/or metrorrhagia. Only twice was such irregularity absent, pain being the occasion for investigating one patient, while routine curettage, accompanying a plastic operation, revealed uterine malignancy in the second instance.

In the postmenopausal group referred to, irregular "spotting" was the most frequent symptom beginning, as mentioned, at varying intervals after the cessation of normal menses, in one case as late as 26 years thereafter. Only 3 of these patients had noticed no postmenopausal bleeding, and in one of these the first sign was a metastatic nodule in the vagina. In a second, pain was the predominant symptom, due to hematometra associated with cervical atresia. In the third instance, the history of absent bleeding seems faulty in retrospect since advanced malignancy was present clinically.

It is astonishing how long symptoms may persist before advice is sought and treatment instituted, but this observation is not unique. In the premenopausal group the duration of symptoms before medical advice was sought averaged from eight to nine months. Reasons for this delay are too well-known to require repetition. It should be empha-

sized, however, that it is in this group that the diagnosis is more likely overlooked or discovered only through routine examination.

Among the postmenopausal patients the average duration of symptoms prior to diagnosis was from twelve to thirteen months. The significance of postmenopausal bleeding is still too little appreciated, not only by the laity but by too many of the medical profession. There has been some slight improvement noted in these particular statistics when compared with our previous report. This is encouraging, and in accord with Miller's impression.

Nonsanguineous discharge is of little value diagnostically in our experience, and we doubt its statistical significance, as do others. Pain, too, is a difficult symptom to evaluate except in relatively advanced cases of fundal carcinoma. The pain can be explained so frequently on other grounds, especially in the presence of associated pelvic lesions, intestinal disturbances and other extrinsic factors. Nevertheless, it should not be entirely discounted, for, as Healy and Brown have pointed out, prognostic significance may be attached to it (Table III).

The occurrence of metrorrhagia and menorrhagia during the premenopausal epoch, and "spotting" or frank bleeding after the establishment of the menopause are of primary significance in directing attention to the necessity of excluding fundal carcinoma; leucorrheal discharge and pain are of less diagnostic importance, but fortunately the presence of these symptoms may influence the patient to seek medical advice.

TABLE III. SIGNIFICANCE AND DURATION OF SYMPTOMS

GROUP	PATIENTS	IRREGULAR BLEEDING	AVERAGE DURATION	DISCHARGE	PAIN
Premenopausal	27	25	8-9 mo.	8	6
Postmenopausal	100	97	12-13 mo.	27	36
Total	127	122		35	42
Per cent	100	96.0		27.5	33.0

Diagnosis and Management

From the foregoing discussion relative to symptomatology, it may be of interest to relate our experiences in the diagnosis of fundal carcinoma and the part that this plays in management and treatment. For a long time we have emphasized the important place that we believe curettage holds as a diagnostic measure. Our procedure has been to employ curettage routinely in practically all of our gynecologic operations, whether or not we suspect the presence of endometrial malignancy. More and more we accompany it with routine biopsy of the cervix and cervical canal, a point to which particular attention has been called in previous publications.

Because of the well-known association of fibromyoma of the uterus and carcinoma, we always regard the sole diagnosis of the former with suspicion, especially in women over forty years of age. In other words, we feel that too often menorrhagia and metrorrhagia are ascribed to the presence of the fibromyoma found upon examination, and that an inadequate plan of treatment is carried out forthwith. Accordingly in women over forty or forty-five years of age, in whom an accompanying carcinoma of the fundus is possible in addition to the fibromyoma present we insist upon preliminary curettage at the time of operation, and have radium available for intrauterine application, especially if our suspicion is enhanced by the gross appearance of the eurented material. At the

same time the cervix and cervical canal are carefully inspected and biopsied as a matter of record. This is in case the uterus is but moderately enlarged, no submucous tumors are present, and we feel that conditions are suitable for irradiation therapy on general principles. The radium is then placed in the uterine cavity (50 or 100 mg. in capsules, singly or in tandem) and a four-hour report secured on the curettings and on the biopsied cervical tissue too, if indicated. If the report is negative for malignancy, indicated dosage for a benign condition is then employed. If, on the other hand, fundal carcinoma is present, adequate dosage is provided, and panhysterectomy with bilateral salpingo-oophorectomy follows in eight to ten weeks, if the patient is a reasonably satisfactory surgical risk. Otherwise radium therapy, sometimes repeated or even associated with external irradiation, is depended upon. This same technique is likewise carried out in patients having postmenopausal bleeding with or without the presence of concomitant fibromyoma, if unaccompanied by adnexal abnormalities.

Conversely, if the uterine enlargement is particularly marked or irregular, if submucous tumors are present, or if accompanying adnexal lesions are present, immediate panhysterectomy and bilateral salpingo-oophorectomy is the procedure of choice. This is also true if the cervix is manifestly abnormal. On the other hand, if supravaginal hysterectomy is thought to be an indicated or safer procedure, the cervix, if abnormal, is treated first by cautery or endothermic resection, together with curettage. The entire question, in our opinion, is one of individualization rather than standardization.

Should carcinoma of the cervix be discovered instead, treatment is with external irradiation primarily, followed by the use of radium locally, disregarding, for the time being at least, any fibromyoma that may be present.

Another factor in the faulty management of women with irregular bleeding, whether pre- or postmenopausal, is the use of external irradiation or even intrauterine radium applications without diagnostic curettage. The assumption that such bleeding is due to functional causes, or to fibromyoma, either present or suspected, is fallacious and productive not only of incorrect diagnosis, but of ill-advised and inadequate treatment. Equally true is the promiscuous and indiscriminate use of hormonal therapy to control irregular bleeding in the pre- and postmenopausal age groups. Even if essential diagnostic curettage precedes the use of hormonal therapy among such women, there seems to be little excuse for this long-continued form of treatment when well-recognized radiological and surgical methods will assure the future security of the patient. The childbearing period has passed, and it is not logical to proceed with hormonal therapy at this time of life. Even estrogenic therapy for the control of the vasomotor disturbances of the menopause may provoke confusing bleeding.

Objections to diagnostic curettage have been voiced by some observers; metastatic lesions developing some time later have been ascribed to it. In spite of this rare possibility, we feel that the advantages far exceed the disadvantages.

In this series 114 patients (89.7 per cent) were suspected of having carcinoma of the fundus, and preliminary curettage confirmed the diagnosis 106 times. It was omitted in 8 suspected cases, all in the postmenopausal group and these patients were all operated upon prior to 1930, immediate panhysterectomy being performed.

Thirteen patients (10.3 per cent) were not suspected of having fundal carcinoma. Diagnostic curettage was performed in 5 of them, all in

the postmenopausal group, and the discovery of malignancy was followed by appropriate treatment.

Of the remaining 8 unsuspected cases not everted, 3 were in the premenopausal group, and supravaginal hysterectomy was performed for fibromyoma, together with adnexal extirpation. Fundal carcinoma was discovered immediately upon removal of the fundus in two of them. The cervical stumps were cauterized from above in both instances, and removed in one, while radium needles were employed in the adjacent broad ligament of the other. This patient recovered from the operation but died 3 months later of pneumonia. The patient in whom the stump was allowed to remain died of peritonitis on the seventh postoperative day. Fundal carcinoma was not discovered in the third patient until the removed fundus was examined routinely in the laboratory. Radium was later applied to the cervical stump.

Five of the 8 unsuspected cases were in the postmenopausal group. In 2 of them bleeding was attributed to prolapse and proclitonia respectively, and vaginal hysterectomy without adnexal extirpation was performed. Postoperative x-ray was used in one. In 2 others supravaginal hysterectomy was performed elsewhere for fibromyoma, the adnexa being removed in one case but not in the other. These patients were both treated with postoperative x-ray. The fifth patient was operated upon because of bilateral ovarian tumors, which were removed and proved to be carcinomatous, secondary to fundal malignancy. Radium to the uterine cavity, and x-ray therapy followed this surgical procedure, which was not followed with hysterectomy because of the patient's poor general condition.

The analysis of these cases indicates clearly the value of careful preliminary study and diagnostic curettage in the management of fundal carcinoma.

Associated Pathology

Table IV relates to the associated pathology encountered. Only those lesions most frequently met with or accurately recorded have been tabulated. Attention may properly be called to the fact that in those patients in whom irradiation therapy alone was employed, accompanying pelvic pathology could not be accurately recognized through bimanual palpation alone.

TABLE IV. ASSOCIATED PATHOLOGY

LESION	PATIENTS	PER CENT
Fibromyoma (surgical cases)	25	37.8
Anemia	31	24.4
Diabetes	14	11.0
Polyps (one malignant)	10	7.8
Pyometra	8	6.3
Concomitant carcinoma	5	3.8
Ovarian tumors	4	3.1
Proclitonia	3	2.3
Previous pelvic procedures	39	30.7

Association with fibromyoma was most frequent, and this is in accord with the findings of others. Healy and Brown, Masson and Gregg, and Norris and Dunne reported approximately the same incidence—35 to 38 per cent. The frequency presented here (37.8 per cent) is based upon the findings in the 66 patients having surgical procedures. The important relationship which these tumors bear clinically to fundal carcinoma has already been discussed.

Secondary anemia existed in only a quarter of the patients. The criterion of this diagnosis was a hemoglobin reading under 70 per cent, and a red blood cell count under 3,500,000. Leucocyte counts over 9,000 were reported in 30 per cent of the patients.

A rather high proportion of diabetics (11 per cent) was encountered and this apparently was a factor in one postoperative death. Smith reported 4 per cent in his recent series. This association between diabetes and carcinoma is not surprising when we consider that the obesity present in so many patients may predispose to, or be associated with, the former disease. The incidence of pyometra and polyps was relatively low, as was that of concomitant ovarian tumors. Concomitant carcinoma was found in the breast, ovary and large bowel (3.8 per cent). Procidencia was found three times, and two of these cases have been reported previously.

The exact incidence of cardiorenal disease has not been computed, neither has the numerical occurrence of obesity. However, these conditions were present in an appreciable number of patients, especially among those women in the older age groups. These handicaps influenced the choice of therapy appreciably.

Previous operative procedures of a pelvic nature were noted in 39 patients, an incidence of 30.7 per cent. Of special interest were the findings in 12 patients, in whom earlier curettage was accompanied with intrauterine radium applications for apparently benign conditions, and endometrial carcinoma was found subsequently in these patients at varying intervals thereafter. Eleven of these cases were reported in detail at a recent meeting of the American Gynecological Society. A similar case has come to our attention since then and is included in this report; an additional patient in the series previously reported upon had received x-ray therapy for fibromyoma of the uterus without preliminary curettage.

It is significant that careful analysis of this group of patients shows that in 6 of them carcinoma was evidently present at the time of the primary curettage and radium application, errors of omission and judgment having been responsible for the delay in adequate treatment. In 4 patients no such criticism seems tenable, the neoplastic process very probably having been a new and independent one. In the remaining 2 patients, the early curettage was of such character that it was referred to by the pathologist, Dr. Jacob Hoffman, as "carcinoid hyperplasia," since it resembled marked hyperplasia very closely, but might well have been regarded by others as adenoma malignum. Eventually frankly malignant lesions were diagnosed in these 2 patients.

Clinical Grouping

Defining the clinical extent of involvement in fundal carcinoma presents more difficulty in classification than does cervical carcinoma. Several plans have been suggested.

That of Schmitz and Schmitz resembles in character their very excellent grouping of cervical malignancy, viz., Groups I and II, relatively small lesions confined to the endometrium with localized but progressive infiltration of the myometrium in varying degree; Group III, advanced infiltration of the uterine wall; Group IV, massive uterine involvement with or without extension beyond its confines. Masson and Gregg follow this grouping.

Healy and Brown prefer the following grouping: I, uterus not enlarged; II, uterus enlarged, but not over size of a 2½ months' gesta-

tion; Group III, extension of carcinoma beyond uterus. Ward quotes this classification in his recent paper.

H. S. Crossen in 1937 presented a rather elaborate grouping divided into six stages, based upon local involvement and varying degrees of more remote extension.

Miller favors this division: Group I (Normal); no palpable enlargement of the uterus; cavity measures 3 inches or less. Group II (Moderately enlarged); enlarged uterus up to $2\frac{1}{2}$ months' pregnancy; cavity measures less than $4\frac{1}{2}$ inches. Group III (Markedly enlarged); uterus size of 3 months' pregnancy or more; cavity measures more than 5 inches. This grouping is modified somewhat after a study of the removed uterus, thus increasing the accuracy of the classification.

From the beginning of our work, we have followed the classification of the American College of Surgeons which is as follows:

1. Primary case
2. Recurrence in vaginal wall after panhysterectomy
3. Recurrence local after panhysterectomy
4. Recurrence remote after panhysterectomy
5. Recurrence after supravaginal hysterectomy
6. Recurrence after irradiation therapy
 - A. Disease limited to uterine cavity
 - B. Disease involving broad ligaments (ovary)
 - C. Vaginal metastasis
 - D. Remote metastasis

It has been our feeling that this grouping is sufficiently broad to classify each patient satisfactorily upon admission for clinical and statistical purposes, for the frequent presence of accompanying fibroma may influence the size of the fundus a great deal. Furthermore, it is sometimes impossible to determine accurately the size of the uterus in the very obese individual. Accordingly, irrespective of the relative size of the uterus, we attempt to decide whether the carcinoma is limited to the organ when we see a patient primarily (IA), or whether the disease has extended beyond it (IB). The remaining groups seen are relatively few. On such a basis, we believe that 91 patients (74 per cent) could be placed in Group IA. Interestingly enough, this percentage is not far removed from Healy and Brown's 71 per cent in Groups I and II, Miller's 69.3 per cent in Groups I and II, Fricke and Bowing's 69.8 per cent; Masson and Gregg's 82 per cent in Stages I, II and III is greater.

Grade of Malignancy

Here again we have departed somewhat from accustomed terminology. Early in our work we realized, as have Meigs, Smith, Miller and others, that the accepted grades of malignancy, so carefully postulated by Ewing, Mahle, Healy, Broders, and Cutler, may be found to exist in different sections or blocks from the same specimen examined. In many instances, too, we found it difficult to decide such classification without question. Accordingly, in 1930, at the suggestion of the late Baxter L. Crawford, former Pathologist and Director of Clinical Laboratories at Jefferson Hospital, we began to divide our fundal carcinomas into three broad groups of malignancy, based on the predominant characteristics of each section examined, as follows:

1. Low grade (corresponding to papillary adenoma malignum and adenoma malignum, Grades I and II).

2. Intermediate grade (corresponding to adenocarcinoma, Grade III).
3. High grade (solid cellular, or diffuse anaplastic adenocarcinoma, Grade IV).

Meigs published a similar grouping in 1934.

In a separate grouping we, of course, place the rarer adenoacanthoma. With the exception of two histologic slides of years ago, that could not be located for review, all the lesions have been classified as outlined (Table V). That any attempt at histologic classification leaves much to be desired, and is subject to vagaries of interpretation, is brought out by comparing these groupings with those of others. This reveals that there is greater conformity in classifying the lower grade lesions than the intermediate ones, and this is also true of the higher grade types of lesions.

TABLE V. GRADE OF MALIGNANCY

GRADE	NUMBER	PER CENT
Low (Grades I and II)	50	39.4
Intermediate (Grade III)	46	36.2
High (Grade IV)	28	22.0
Adeno-acanthoma	1	0.8
Unclassified	2	1.6

Type of Treatment

Table VI, summarizing the different methods of treatment employed, requires clarification. Between 1921 and 1929, patients were treated either by surgery alone or by irradiation, and more of the latter were treated with radium only, than with external irradiation in addition. Beginning in 1929 preliminary irradiation with radium began to be used prior to surgery in a few cases, followed in some instances with post-operative x-ray therapy. At the same time x-ray therapy followed the use of radium almost uniformly in those patients selected for irradiation only. Since 1937, however, the indications for preliminary irradiation with radium followed by surgery have been extended more and more, while irradiation therapy alone has been used less frequently. Post-operative x-ray therapy, in patients that have been operated upon after a preliminary radium treatment, is used only when there is definite evidence of extension of disease outside the uterus or in cases of recur-

TABLE VI. TYPE OF TREATMENT

YEARS	PATIENTS SEEN	PATIENTS TREATED	SURGERY	IRRADIATION	SURGERY AND IRRADIATION
1921 to 1937	75	74	11	37	26
Per cent			14.9	50.0	35.1
1937 to 1942	52	52	5	23	24
Per cent			9.6	44.2	46.2

rence; neither do we favor it as a preliminary procedure, as does Miller, for we prefer radium instead. Likewise, since 1929, surgery alone has been employed but a few times in specific instances. Accordingly, we have divided the tabulation according to the years designated for reasons of comparative study. Few patients treated between September 1, 1937, and September 1, 1942 are yet eligible for an appraisal of five-year end results.

Results of Treatment

The end results of treatment will be discussed under several topics:

1. Comparative results with each type of treatment.
2. Composite result with all types of treatment expressed in absolute and relative figures.
3. Comparative results in relation to grade of malignancy and type of treatment.

Treatment With Surgery Alone.—Part I of Table VII shows the percentage of patients living today (27.2 per cent), as well as the five-year salvage (36.3 per cent) in the group operated upon prior to September 1, 1937. The immediate mortality in this small group of 11 patients was relatively high (18.1 per cent) and the cause of the deaths is stated in the table.

TABLE VII. TREATMENT WITH SURGERY ALONE

1. Patients treated, 1921 to 1937	11		
Alive, 11 to 18 years	3	—27.2 per cent	{Five-year salvage—4, 36.3 per cent
Survived 5 years	1		
(Noncarcinoma death—1)			
Postoperative deaths			
(Cardiodiabetic, 12th day)			
(Peritonitis, 7th day)	2	—Mortality	18.1 per cent
Died of carcinoma, 1 to 4 years	5		
2. Patients treated, 1937 to 1942	5		
Alive, 1 to 3 years	4		
Postoperative deaths	0	—Mortality	
Died of carcinoma, 1 year	1	(combined),	12.5 per cent

Of the 4 five- to eighteen-year survivors, 2 had preliminary curettage for diagnosis, followed by abdominal panhysterectomy and adnexal extirpation; 2 had similar procedures without preliminary curettage.

Of the 5 patients succumbing within 1 to 4 years of operation, one had a vaginal hysterectomy without removal of the adnexa (unsuspected case); 2 had immediate complete abdominal surgery without preliminary curettage; 2 had preliminary curettage; with supravaginal hysterectomy in one because the complete operation was technically impossible, while marked pelvic extension of disease prevented complete surgery in the other.

With regard to the 2 patients who died postoperatively, one had preliminary curettage followed by complete abdominal surgery, with the handicap of diabetes and cardiac disease. The second patient, aged 47, was operated upon supravaginally for a fibromyoma, and no preliminary curettage was done. When fundal carcinoma was discovered, the cervical stump was cauterized from above, both adnexa were removed, but fatal peritonitis developed several days thereafter. The course of the latter patient is illustrative of the pitfalls encountered when fibromyomata are regarded as the sole lesion concerned.

Surgery alone was not employed for any patient between 1932 and 1939. Since then surgery alone has been performed on 5 patients, as shown in part 2 of Table VII for comparative reasons. One, aged 54, had a huge fibromyomatous uterus, and the presence of accompanying endometrial carcinoma was considered. Curettage was suspicious and immediate panhysterectomy with adnexal removal was carried out, the removed uterus showing carcinoma. Three other patients had received radium for benign conditions 4 to 10 years previously, and the return

of symptoms was promptly followed by complete abdominal surgery. The fifth patient, aged 68, had an examination under anesthesia and a diagnostic curettage because of postmenopausal bleeding. An indistinct pelvic mass was felt and the curette perforated a friable uterine wall. Immediate abdominal section showed widespread carcinomatosis secondary to fundal malignancy, and nothing else was done, the patient dying 3 months later. The remaining 4 patients are alive and well, and present a favorable trend toward five-year survival or better.

Far better comparative results with surgery alone have recently been reported by Smith (58.8 per cent), Ward (63 per cent), Norris and Dunne (47.8 per cent).

Treatment With Irradiation Alone.—Part I of Table VIII shows the percentage of patients living today (18.9 per cent), and in addition the five-year salvage (40.5 per cent) in the group of patients treated solely with irradiation prior to September 1, 1937. There was no primary mortality. Sixteen of the group were treated with radium only, 20 with x-ray in addition, and one with x-ray only, a total of 37. Eleven of these had repetition of treatment, a factor that increased the five-year survival rate appreciably in over half of them. The x-ray therapy has been administered under the supervision of the late Dr. W. F. Manges, Dr. J. T. Farrell, Jr., and Dr. K. Kornblum.

TABLE VIII. TREATMENT WITH IRRADIATION ALONE

1. Patients treated, 1921 to 1937	37	
Alive, 5 to 14 years	7—18.9 per cent	{ Five-year salvage—15, 40.5 per cent
Survived, 6 to 15 years (Noncarcinoma deaths—6) (Died of carcinoma—2)		
Postoperative deaths	0	
Died of carcinoma, 1 to 4 years	22	
2. Patients treated, 1937 to 1942	23	
Alive, 1 to 4 years	16 (9—4 years; 3—3 years)	
Postoperative deaths	0	
Died of carcinoma, 1 year	7	

An intrauterine radium dosage of 2,400 to 3,600 mg. hours was rarely exceeded prior to 1937, employing a 50 mg. capsule screened with 0.3 mm. silver and 1.0 mm. of brass, enclosed in black rubber tubing, 2.0 mm. in thickness; 12.5 mg. needles, screened with 0.3 mm. of Monel metal, also enclosed in black rubber tubing, were frequently used additionally in a tandem arrangement. Later on a 50 mg. capsule screened with 0.5 mm. of platinum was also employed. External irradiation usually averaged 1,500 R. to each of 4 portals. In the majority of instances surgery, either immediately or following irradiation, was contraindicated because of the extent of the disease, obesity, cardiovascular or other systemic disturbance, but four patients, seemingly good operative risks, objected to subsequent hysterectomy, and they have survived from 8 to 14 years.

Part 2 of Table VIII shows that since 1937 irradiation therapy alone has been employed in 23 patients, 10 times with radium alone and 13 times with x-ray in addition. Two or three 50 mg. capsules of radium, screened with 1.5 mm. of platinum, and enclosed in 2.0 mm. black rubber tubing, are employed in tandem and the average dosage varies from 3,600 to 5,000 mg. hour. External irradiation, when used, averages 1,500 to 2,000 R. to each of 4 portals. There has been no immediate mortality.

Frequently we have been prejudiced against subsequent surgery because of extent of disease or physical contraindications, and in some of these instances the clinical response has been remarkably favorable. Five of this group of patients are among those previously mentioned as having received radium treatments from 2 to 12 years previously for apparently benign conditions. In each instance carcinoma was evidently present but undiscovered at the time, the radium therapy was accordingly inadequate in amount, and the advantage of subsequent surgery was denied the patient as well. An excessively obese patient should be mentioned particularly because for many years she had been considered as an endocrine problem, an earlier curettage having shown hyperplasia. Continued irregular bleeding finally resulted in another curettage, and the carcinoma then discovered has been twice treated with radium. On the basis of what we have learned from an analysis of this group of irradiated patients we feel that whenever possible such a patient should have the advantage of subsequent surgery, as will be emphasized later. On the other hand, when physical factors make subsequent operative treatment particularly hazardous, much can be expected from irradiation therapy, and the trend of our present 3- and 4-year survivals bears this out. The desirability of repeated test curettage and secondary radium applications in appropriate cases should not be lost sight of either, as this has proved effective in several of the patients in this group. The gratifying 5-year end results obtained with irradiation therapy in patients falling into a group such as this have been reported by Norris and Dunne (43.8 per cent), Fricke and Bowing (39 per cent), Healy and Brown (39 per cent), Miller (37 per cent) and Ward (32 per cent).

Treatment With Surgery and Irradiation.—It will be seen from Table IX that relatively more patients have been subjected to a combined type of therapy since 1937, than between 1921 and 1937. As previously stated it was not until 1929 that the plan of preliminary irradiation began to be put into effect more generally, using the newer irradiation technique just described.

Part I of the table shows the present-day survival of patients treated prior to September 1, 1937 (15.3 per cent) together with the five-year salvage up to that time (38.4 per cent). There was no operative mortality. A brief summary of the sequence of treatment of these patients with results follows:

TABLE IX. TREATMENT WITH SURGERY AND IRRADIATION

1. Patients treated, 1921 to 1937	26	
Uteri removed (10—prelim. radium)	21	
Alive, 5 to 16 years	4	15.3 per cent (Five-year salvage—10,
Survived, 5 to 11 years	6*	19.0 per cent 38.4 per cent)
(Nonearcinoma deaths—2)		corrected) * (42.9 per cent cor-
(Carcinoma deaths—4)		rected)
Postoperative deaths	0	
Died of carcinoma, 1 to 4 years	16	
2. Patients treated, 1937 to 1942	24	
Uteri removed (20—prelim. radium)	23	
Alive, 1 to 4 years	23	(4—4 years, 5—3 years)
Postoperative deaths	0	
Died of carcinoma, 1 year	1	

Uteri removed after preliminary radium—30

Residual carcinoma absent in 15 and present in 15 (50 per cent each)

*Corrected for the 21 Uteri Removed.

a. Eight of the patients in this group had preliminary irradiation with radium according to a positively arranged plan, of whom 4 survived from 7 to 10 years, with 2 alive and well at present.

b. Five patients had complete abdominal surgery, followed by x-ray therapy, one of whom has survived for 16 years.

c. Four patients had supravaginal hysterectomy followed by x-ray therapy in two cases, and by radium placed in the cervical stump, and in the right broad ligament base in the third and fourth ones respectively (unsuspected cases). Three survived from 7 to 13 years, and one of these patients is alive now, while the fourth died 3 months after treatment.

d. Two patients had received radium treatments several years before carcinoma became evident, supposedly for benign conditions, and both died within a year of hysterectomy, in spite of postoperative x-ray.

e. Two patients had vaginal hysterectomy without removal of the adnexa. In one, the diagnosis was unsuspected in an operation for procidentia, which was followed by x-ray therapy and 3-year survival. In the other, two courses of radium therapy were given primarily because of the patient's poor general condition. Later on she was prevailed upon to be operated upon elsewhere, a procedure that she survived 4 years.

f. In 5 patients the uterus was not removed at operation, because of advanced disease or complicating pathology necessitating simpler procedures. Radium had been used some time before in one patient, immediately after the exploration in another, and just preceding an unexpected abdominal section of a third, when an ovarian cyst was discovered during examination under anesthesia. This proved to be carcinomatous and carcinoma of the rectosigmoid was found also, these lesions requiring oophorectomy and bowel resection. It was thought that each lesion was a primary one and postoperative x-ray therapy followed. Only one of these patients survived the 5-year period, but she died of carcinoma. In the remaining 2 of these 5 patients exploratory operation only was done, after an earlier radium treatment in one case and with subsequent x-ray therapy in the others. Neither patient survived a full year.

It would seem reasonable, therefore, to correct the 5-year survival rate for surgery by eliminating the 5 patients in whom it was impossible to remove the uterus when surgery was attempted. On this basis the corrected 5-year salvage rate for 21 patients would be 42.9 per cent, with a comparative percentage of 45.4 for those having preliminary irradiation and a percentage of 40 for those patients whose irradiation therapy was subsequent to surgery.

Outstanding 5-year end results have been reported by Miller (82.3 per cent), Smith (66.2 per cent), Ward (64.9 per cent) and Healy and Brown (55 per cent) employing combined surgical and irradiation therapy. Heyman, long an ardent advocate of irradiation therapy, is not inclined at present to prefer it to the exclusion of surgery, except when the latter is definitely contraindicated.

Part 2 of Table IX shows a much more systematic use of preoperative irradiation with radium since September 1, 1937. In 20 of the 24 patients in the group treated since that time preliminary radium therapy has been followed with complete abdominal surgery in 19 patients and with vaginal surgery in one.

The four exceptions to this plan might be noted to advantage. In one, a patient aged 62, immediate complete abdominal surgery was per-

formed for a huge fibromyomatous uterus, and x-ray therapy was employed afterward when extensive carcinoma was discovered in the removed uterus. In a second patient, aged 54, carcinoma of the uterus was not suspected primarily, the patient being operated upon because of ovarian cysts. They were found to be carcinomatous, but because of the feeble condition of the patient, the uterus was not removed too, and subsequently x-ray therapy and radium in the uterus were employed. Two patients were sent to us after supravaginal hysteromyomectomy elsewhere, without preliminary curettage, when carcinoma was found in the removed uteri. They were each given x-ray therapy. There was no operative mortality in this series, and thus far only one patient has died of carcinoma. This fortunate circumstance reduces the post-operative mortality for the entire series to 3.03 per cent. The present trend of the 3- and 4-year survivals is satisfactory.

Taking into consideration 30 patients in whom the removed uterus was available for study following a plan of preliminary radium therapy, residual carcinoma was present 15 times (50 per cent) and absent 15 times (50 per cent), although in one of the latter patients metastasis was found in one ovary. These findings are enlightening in view of the recent excellent report of Donovan and Warren. These observers found that in only 5 of 46 patients similarly treated was residual carcinoma absent, an incidence of 11 per cent. The report of Healy and Brown is based on 75 cases, but in 6 of these external irradiation only was used, so that of 69 patients receiving preliminary radium therapy, residual carcinoma was absent in 28, or 40.5 per cent. Corseaden's incidence in 21 cases was 38 per cent; in Smith's cases it was 16.6 per cent.

With relation to intrauterine radium dosage, residual carcinoma was absent in 7 of 9 patients in our series who received an intrauterine dosage of 4,000 to 5,000 mg. hr., or 77.7 per cent. Healy and Brown's figure was 60 per cent with a dosage of 3,400 to 4,000 me. hr., approximating ours. Friedman, employing 4,000 to 8,000 mg. hr. with his ingenious hystero-stat treatment, found absence of residual carcinoma in 7 of 8 patients thus treated (87.5 per cent). In the series reported by Donovan and Warren, 2 of the 5 removed uteri showing no residual carcinoma had been subjected to a radium dosage averaging 3,500 to 4,000 me. hr.

Our reason for advocating the preoperative use of radium is not based on the assumption that it will eradicate the disease, for whenever possible we plan to follow the application in 8 to 10 weeks with complete surgical removal. It is pretty well recognized, as Sampson and others have pointed out, that radium applications to the uterine cavity may be ineffective because of irregularities in the nature and position of the growth, often influenced by pressure of concomitant fibromyoma, or other abnormalities that may cause peculiar deviations. We agree with Healy and others that the local growth is devitalized by the action of the radium and thus less likely to be disseminated through lymph and blood channels. Furthermore, we feel that local infection is also diminished thereby. Added to these reasons is our observation that patients treated by the combined plan of therapy have responded more satisfactorily than those treated by surgery alone. The fact that residual carcinoma is found in one-third to one-half of the removed uteri only stresses the force of the decision to follow through with complete surgery whenever the condition of the patient permits.

On the other hand, permanently satisfactory applications of radium must certainly be made in numerous instances. This is borne out by the

absence of residual carcinoma so often, and by the destruction of the endometrial lining of the uterine cavity. Again, certain patients suspected of having fundal carcinoma do not have it. The application of radium in suitable dosage, when the report of the curettage is benign, will benefit such patients, who thus escape unnecessary radical surgery. Finally, if subsequent surgery is definitely contraindicated, and irradiation must be relied upon, we know from our experience that the clinical response may be very gratifying.

In summary, therefore, we feel both from our related experience, and from that of others, that preliminary irradiation with radium prior to complete surgery is rational treatment for carcinoma of the fundus, but we are frank to admit that the results of a further observation period may alter our present opinion.

End Results With All Types of Treatment

In estimating the curability of cancer we are judged, not entirely by the specific plans of therapy that we favor or endorse, but by end results as a whole. To be thoroughly comprehensive, such an estimate must depend upon absolute and relative figures, based upon an accurate follow-up, with mention of untreated patients. Percentages based upon varying types of treatment are valuable for comparison and serve the purpose of showing what such procedures accomplish, but these figures do not tell the whole story, which may sometimes be very discouraging. On that basis the 5-year end results are depicted in Table X. The present-day survival is 18.6 per cent absolute, and 18.8 per cent relative. Six years ago the figures were 25.5 and 26.0 per cent respectively. This apparent decline of survivors must take into consideration the fact that fundal carcinoma embraces an older age group, and that as years go by the earlier survivors will succumb to the intercurrent diseases of the aged. Excluding noncarcinoma deaths, the 5-year salvage rates are 33.3 per cent absolute and 33.7 per cent relative, and these are comparable to the former figures of 31.9 and 32.6 per cent respectively. Finally, the figures of total 5-year salvage are 38.6 per cent absolute and 39.1 per cent relative, almost exactly the same as those presented 6 years ago (38.0 and 39.1 per cent respectively). Whether a future report will show improvement depends upon whether or not the present favorable trend of the 3- and 4-year survivals is maintained.

Other recent percentages presented on a similar basis are those of Ward (44.4 and 47.4); Norris and Dunne (44.5 and 46.1); Smith (54.8, 56.0 and 56.2 for 3 distinct observation periods); Miller (55.8).

TABLE X. END-RESULTS, ALL TYPES OF TREATMENT, 1921 TO 1937

Patients seen		75		
Patients treated		74		
Follow-up		100 per cent		
PATIENTS	NUMBER	PER CENT ABS. SALVAGE	PER CENT REL. SALVAGE	
Alive 5 to 18 years	14	18.6	18.8	
Corrected for noncarcinoma deaths, 5 to 15 years	25	33.3	33.7	
Five-year salvage, including carcinoma deaths, 5 to 8 years	29	38.6	39.1	
Patients seen and treated, 1937 to 1942		52		
Living 1 to 4 years after treatment		43—82.6 per cent		
Died within 1 year of treatment		9		

Relationship of Grade of Malignancy to Type of Treatment.

We feel that middle ground must be taken when the relationship of the histologic picture to therapy and prognosis is considered. The grade of the particular tumor secured by curettage in the suspected case is only one factor upon which to base treatment and prognosis. More important are the physical status of the patient, the duration of the symptoms and the extent of the disease. The idea long prevalent, that high grade or anaplastic types of malignancy are radiosensitive and that low grade ones are radioresistant, has surely been disproved by workers in the field. Warren's statement that radiosensitivity and radiocurability are not equivalent terms is acceptable in the light of the experience of most of us. It is well to keep in mind the effect of the constantly changing relationship that exists between irradiation and the diverse processes of cellular life, both abnormal and normal. In other words, the response to irradiation is very probably dependent not only upon the biologic processes that are constantly going on in all the tissues within range of treatment, but also to an appreciable extent upon the age and physical status of the patient. The amount of irradiation administered must also be taken into consideration. That is why one cannot predict with certainty what is going to happen to the irradiated lesion until we have observed the clinical response. This is borne out by the fact that low grades of fundal malignancy do respond well to irradiation in many instances, while the reverse is sometimes true where intermediate and high grade lesions are concerned.

In Table XI we have tabulated the 5-year end results in relation to the grade of malignancy and type of treatment. No unalterable conclusions can be drawn but the course of events can be pointed out. Equally good results in low grade lesions were secured with both surgery and irradiation, but in combination the survival rate was greater. Of the 15 uteri removed surgically after preliminary radium, in which there was no residual carcinoma, the previous curettage had shown low-grade lesions in twelve. In the intermediate and high-grade lesions, irradiation, both alone and in combination with surgery, was more advantageous than surgery alone. A similar study of the patients treated less than 5 years ago has not been made at this time.

TABLE XI. FIVE-YEAR END RESULTS IN RELATION TO GRADE OF MALIGNANCY AND TYPE OF TREATMENT

GRADE	SURGERY	IRRADIATION	SURGERY AND IRRADIATION	5-YEAR SALVAGE
Low (Grade I-II) 23	2 out of 4 50 per cent	5 out of 11 45.4 per cent	6 out of 8 75 per cent	13 56.5 per cent
Intermediate (Grade III) 30	1 out of 5 20 per cent	5 out of 15 33.3 per cent *(Corrected)	3 out of 10 30.0 per cent 28.5 per cent	9 30.0 per cent
High (Grade IV) 19	0 out of 1 0.0 per cent	5 out of 11 45.4 per cent *(Corrected)	1 out of 7 14.2 per cent 16.6 per cent	6 31.5 per cent
Unclassified 2	1 out of 1 100.0 per cent	-----	0 out of 1 0.0 per cent	1 50.0 per cent
Total 5-yr. salvage 74	4 out of 11 36.3 per cent	15 out of 37 40.5 per cent *(Corrected)	10 out of 26 38.4 per cent 42.9 per cent	29 39.1 per cent

*Corrected for the 21 uteri removed.

We have been much disturbed by the lesion referred to as "carcinoid hyperplasia," an atypical endometrial hyperplasia, that might be regarded by some as an extreme degree of hyperplasia and by others as a papillary adenoma malignum. Mitotic activity is present in the stroma cells. The glandular structure is not only markedly increased, but an extreme disparity in size occurs, as in true hyperplasia. At times these glandular areas present bizarre convolutions, and they are lined by several rows of cells showing mitotic activity. Proliferation of the cells may be so distinct that resulting polypoid formations may extend into the lining of the glands. Stromal elements are lacking and this causes the glands to approximate each other almost to the point of fusion. Several of these lesions have been encountered and referred to in this and a previous contribution. From this experience we are inclined to place it in the category of a low-grade malignancy and treat it accordingly.

Summary and Conclusions

1. A consecutive series of 127 patients having carcinoma of the fundus has been studied with respect to diagnosis, management and treatment. Of this group, 75 are eligible for comparative analysis of 5-year end results. There are no untraced patients.

2. Four out of 5 women had already passed their menopause (78.7 per cent) when the diagnosis was made and treatment instituted. The average age of this group was 58.9 years, and the diagnosis was suspected correctly in 90 per cent of the patients because of the postmenopausal bleeding alone.

3. In the premenopausal group (21.3 per cent) the average age was 46.3 years. In 10 per cent carcinoma was not suspected. It is among these younger women, who have not ceased menstruating, that irregular bleeding is too often regarded as benign in origin, and ill-advised or inadequate treatment results. In this regard may be mentioned indiscriminate hormonal therapy, instituted before organic disease has been eliminated, or employed when more radical methods would, in truth, be conservative and life-saving. Abnormal uterine bleeding, then, was the most significant and reliable symptom in 96 per cent of the entire series.

4. The value of diagnostic curettage is apparent, for omission of the procedure was especially costly in certain instances. No known ill results followed its use.

5. Fibromyomas were noted in approximately 38 per cent of all patients treated surgically, and palpation suggested their presence in a number of irradiated patients. Previous pelvic operative procedures had occurred in nearly 30 per cent of all the patients.

6. Carcinoma was thought to be limited to the uterus in 74 per cent of the patients when they were first seen, irrespective of the size of the uterus.

7. It is not a simple matter to establish a decisive gradation of malignancy in every case. Not infrequently the picture is a varied one. For that reason we have chosen the broad and somewhat simplified classi-

fication that has been described. No absolute conclusions can be drawn with regard to the relationship of the grade of malignancy to the type of treatment, but the clinical evidence in this series confirms, in several respects, the observations of others. Low-grade lesions respond equally well to irradiation and surgery, but it would seem that the survival rate in intermediate and high-grade lesions is materially improved where irradiation has been a factor in the treatment, either singly or in combination with surgery. Prognosis based on the grade of malignancy alone is uncertain; it is only one of various factors that must be considered; with irradiation therapy it is the clinical response of the lesion that counts most of all.

8. The various methods of treatment used have been described in detail, with presentation of the relative 5-year end results respectively, as follows: A. Surgery alone, 18.1 per cent; B. Irradiation alone, 40.5 per cent; C. Surgery and irradiation, 38.4 per cent. (Corrected for uteri actually removed, 42.9 per cent.) Irrespective of the type of treatment, the 5-year end results are 38.6 per cent absolute and 39.1 per cent relative.

9. A careful analysis of our earlier experience, combined with the encouraging response to the more recent and systematic plan of procedure described, has convinced us that preliminary irradiation with radium, followed by complete operation 8 to 10 weeks later, is the treatment of choice in carcinoma of the fundus. The procedure employed, and the reasons for it, together with certain exceptions and contraindications that may prevail, have been discussed in detail.

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INTRAVENOUS PYELOGRAMS IN NORMAL AND ABNORMAL PREGNANCIES*

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DILATATION of the ureter in pregnancy has been repeatedly recognized in the past hundred years. The first descriptions were those of autopsy findings: later, with the development of cystoscopy and retrograde pyelography, such changes were demonstrated in the living subject. Objections to this form of investigation were the irritating effect of ureteral catheterization, the danger of artificial overdistention of the urinary passages by the retrograde introduction of dye, and the probability that the picture produced under these circumstances might be largely artefact. With the introduction of intravenous pyelography these difficulties could be avoided.

Schumacher¹ was the first to take advantage of the new technique in studying pregnant women. In 100 such women in various stages of pregnancy and the puerperium, who were free of urinary tract infection, he was able to demonstrate the presence of dilatation, tortuosity and lateral displacement of one or both ureters and dilatation of one or both renal pelves in all women with term pregnancies. The ureter in the pelvis was involved in only two instances. Some hypotonia could be observed in all patients by the fifth (lunar) month. He felt that these phenomena could best be explained by compression and displacement of the hypotonic ureter by the gravid uterus, and that the right ureter was more frequently involved because the left was protected by the sigmoid. In his experience the shape of the pelvis and the presentation and position of the fetus had no significance. He observed no difference in relation to parity, although Duncan and Seng² in 1928, using retrograde pyelography, had concluded that "the multiparous woman showed these conditions earlier, more frequently and in a more marked degree than the primipara." Kretschmer, Healy and Ockuly,³ in a series of forty-four obstetrically urologically normal patients, found 100 per cent dilatation of ureters and pelves, always above the pelvic brim.

Lee and Mengert⁴ confirmed these findings and pointed out that the dilatation begins to regress promptly post partum. They showed that catheter drainage of the ureter for twenty-four hours produced no reduction in dilatation, which seemed to contradict the obstruction theory of causation. Baker and Lewis⁵ compared the findings in a series of pregnant women (number of cases not given), and in twenty-three patients with ovarian cysts or uterine fibromata, in sixteen of whom the tumors

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were large enough to be comparable in size to advanced pregnancy. In pregnancy they found dilatation of the upper urinary tract in 92 per cent, of the right side only in 40 per cent and both sides in 52 per cent. The dilatation was only present after the uterus rose into the abdomen. In the group of patients with large tumors the statistics were similar. The dilatation promptly regressed following delivery or removal of the tumor. From this they concluded that the phenomena could be explained entirely on the basis of mechanical obstruction.

Hundley et al.^{6a and 6b} felt, in contrast to Duncan and Seng, that "the dilatation of the urinary tract occurred later in the primipara than in the multipara, whereas the dilatations were more marked in the former than in the latter group."

Woodruff and Milbert⁷ studied 60 normal pregnant women both ante and post partum and found that by the ninth day after delivery only 20 per cent (twelve patients) had failed to return to normal.

In 1936 Traut and McLane⁸ investigated a group of normal women, twenty-seven of whom were pregnant or puerperal and seven of whom were nonpregnant controls, by means of retrograde pyelography and the Trattner hydrophorograph. With this instrument they were able to demonstrate rhythmic peristaltic activity in the nonpregnant ureter, which was definitely altered by pregnancy as early as the third month, with diminished amplitude of the peristaltic wave. This change reached its peak during the seventh to eighth month, with an increase in irritability during the last month. They concluded that this decreased activity of the ureter could not be explained on the basis of dilatation, but rather that the dilatation probably resulted from ureteral atony, which, they felt, was not caused by any mechanical factor but rather by some as yet undetermined chemical mechanism. Hundley, Diehl and Diggs⁹ following up this line of investigation, treated eight normal women with proluton and pranone for nine weeks, and noted a gradual decrease in peristaltic waves, the diminution in amplitude increasing with the duration of treatment. A similar group, given stilbestrol daily for ten weeks, developed marked peristaltic activity which increased with the duration of therapy. Van Wagenen and Jenkins¹⁰ in a very interesting experimental study on monkeys, were able to show that hydroureter and other changes occurred in these animals also, that the changes were most marked in the first pregnancy and tended to decrease in each successive pregnancy. They also demonstrated, by a series of experiments in which the fetus was removed but the placenta remained in situ, that the changes were dependent on the presence of a functioning placenta and were not the result of mechanical obstruction. They were unable to alter the changes by the administration of either estrogen or progesterone, but thought this might be a matter of dosage.

Experimental

The present study was undertaken in an attempt to determine whether toxemia of pregnancy and urinary tract infection in pregnancy would have any significant effect upon changes in the urinary tract generally accepted as physiologic.

A group of 108 women in various stages of pregnancy and the puerperium have been studied by means of intravenous pyelography.

TABLE I. NATURE OF THE CASES STUDIED

DIAGNOSIS	NUMBER OF CASES	
	PRIMIPAROUS	MULTIPAROUS
Eclampsia	5	1
Severe pre-eclampsia	8	1
Mild pre-eclampsia	3	1
Unclassified toxemia	8	5
Cardiovascular disease	1	20
Pyelonephritis	4	9
Toxemia with pyelitis	2	9*
Eclampsia with pyelitis	2	1
Hyperemesis gravidarum	0	2
Acute nephritis	1	0
Placenta previa	0	1
Polycystic kidneys	1	0
Cushing's syndrome	1	0
Normal	16	7
Total	52	57

*Includes one patient who had acute nephritis with her first pregnancy.

Diodrast was used throughout. The distribution of the cases by parity and diagnosis is shown in Table I. It will be observed that in 85 of these patients pregnancy was in some way abnormal; twenty-three patients, however, were entirely normal as far as could be ascertained. The scatter as to duration of pregnancy in relation to x-ray is great, as the x-rays were taken at the patient's convenience rather than ours.

In all, 113 pyelograms were taken. Five patients were examined twice. In this group one patient was examined both ante and post partum and one patient was examined post partum in both the first and second pregnancies. These are both recorded twice. The other three patients were each examined twice post partum in the same pregnancy, and as the findings did not change the results are recorded only once each.

In six cases, four multiparas and two primiparas, the x-rays were unsatisfactory, as the result of poor preparation or poor concentration of the dye or both. This group is not included in the tabulation. It comprised three patients with hypertensive vascular disease, one with severe pre-eclampsia, one with placenta previa and one with Cushing's syndrome. In this group was seen the only untoward reaction: a multipara with hypertensive vascular disease had a severe shaking chill fifteen minutes after the administration of 5 c.c. of dye.

The results of the x-ray findings are tabulated with respect to parity and time in relation to delivery. All patients whose pregnancy was complicated by toxemia or urinary tract infection are listed as abnormal; the normal group comprises only those patients whose pregnancy was completely uneventful clinically. All those patients who by x-ray had dilatation of the renal pelvis, dilatation, tortuosity and lateral displacement of the ureter are listed as positive. Those who had none of these changes are listed as negative, although two had urinary tract anomalies and one had a stone.

Ante-partum Findings

Unfortunately there are only two normal patients in the ante-partum group (Table II). The primipara, at thirty-three weeks, is negative.

TABLE II. PYELOGRAMS IN NORMAL PREGNANCY

DURATION OF PREGNANCY		PRIMIPAROUS		MULTIPAROUS	
		NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
Ante partum	24 weeks				1
	33 weeks	1			
Post partum	8 days	2			
	9 days	6	3	1	
	10 days		2	3	
	13 days		1		
	3 months	1			
	6 months			1	
	8 months	1			
Total		11	6	5	1

The multipara, at twenty-four weeks, is positive. In the total abnormal group there are twenty-two patients (Table III). Of these seventeen

TABLE III. PYELOGRAMS IN ABNORMAL PREGNANCIES

DURATION OF PREGNANCY		PRIMIPAROUS		MULTIPAROUS	
		NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
4 to 8 weeks				1	
8 to 12 weeks				2	1
12 to 16 weeks				2	1
16 to 20 weeks	1				3
20 to 24 weeks			1		1
24 to 28 weeks			2		2
28 to 32 weeks			1		1
32 to 36 weeks			1		1
36 to 40 weeks					1
Total		1	5	5	11

POST PARTUM		PRIMIPAROUS		MULTIPAROUS	
		NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
4 days				1	
6 days			1		
7 days					1
8 days			1		
9 days			1	5	1
10 days	2		4	4	3
11 days	1		1	1	1
12 days					2
14 days					1
3 weeks	1		2	2	1
4 weeks	1		1	2	1
5 weeks	1		1	2	
6 to 8 weeks	3		3	2	
3 months	3				1
4 months				1	
Total		12	15	20	12

are positive. It is of interest, however, that of the group of seven patients examined between the eighth and the sixteenth week, five are negative and only two are undoubtedly positive, confirming previous

observations that change does not ordinarily begin until the sixteenth week or later.^{1, 5-6} After the sixteenth week, of fifteen patients in the abnormal group, all but one, a primipara, show changes. The group affords no adequate opportunity to contrast the effects of parity.

Post-partum Findings

In the normal group (Table II) there are twenty-one patients, five multiparas, all negative, and sixteen primiparas, of whom all but six are negative. These observations begin as early as the eighth day and include three between three and eight months. The findings confirm those of previous observers that regression is prompt in normal pregnancy. Although the group is small, the fact that all the multiparas have involuted and six of sixteen primiparas have not suggests that parity may influence these changes to some extent, as indicated previously.^{6, 10}

In the abnormal group (Table III) there are 59 patients, twenty-seven primiparas and thirty-two multiparas. Of this total group twenty-seven are positive and thirty-two are negative. Of twenty-seven primiparas fifteen are positive and of thirty-two multiparas twelve are positive. Examinations range from six days to four months post partum, about a third being concentrated on the ninth and tenth days. There is again a suggestive but not conclusive difference in relation to parity.

Urinary Tract Infection and Pyelitis

The patients with urinary tract infection or pyelitis have been tabulated separately (Table IV) in addition to being included in the total

TABLE IV. PYELOGRAMS IN URINARY TRACT INFECTION AND PYELONEPHRITIS

DURATION OF PREGNANCY	PRIMIPAROUS		MULTIPAROUS	
	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
8 to 12 weeks				1
12 to 16 weeks			1	
16 to 20 weeks				2*
20 to 24 weeks		1		1*
24 to 28 weeks		2		1
28 to 32 weeks		1		
Total		4	1	5

POST PARTUM	PRIMIPAROUS		MULTIPAROUS	
	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
7 days				1*
9 days			2	
10 days			1	2*
11 days			1*	1*
12 days			1	
3 weeks		1*		1
4 weeks		1*	1*	
6 to 8 weeks	1			
3 months	1			
4 months			1	
Total	2	2	7	5

*Numbers in italics represent urinary tract infection without pyelonephritis.

abnormal group. Our criteria for the diagnosis of pyelitis are as follows: chills, fever, backache, leucocytosis, kidney tenderness and urine containing white cells and bacteria. The diagnosis, urinary tract infection, implies pyuria—that is, urine containing white cells and viable organisms—without necessarily any symptoms. In the broad sense such a term may also include frank pyelitis. The two diagnoses are separated by the symbols on the chart but are grouped together for purposes of discussion. There are more multiparas than primiparas among the cases of frank pyelitis and also among those of urinary tract infection. The trend noted in the total abnormal group is exaggerated in the infected cases. No conclusion can be drawn about the ante-partum cases, since nearly all of the pregnancies are of sixteen weeks or more, when change might reasonably be expected, but it is perhaps noteworthy that of four pregnancies under twenty weeks three are positive. In the post-partum group are three primiparas, two of whom are positive at three and four weeks, when complete involution could ordinarily be expected, and twelve multiparas of whom five are positive.

Urinary Tract Anomalies

In this group of 108 patients one major and one minor urinary tract anomaly were found. One patient, otherwise normal, had bilateral polycystic kidneys. One patient with mild pre-eclampsia had a bifid pelvis and ureter on the right.

In one patient with eclampsia a calculus of the upper pole of the right kidney was discovered. In none of these was there any evidence of infection.

Discussion

In summary, in twenty-three normal pregnant and puerperal women intravenous pyelography revealed the ante-partum changes usually associated with pregnancy. Post-partum studies in this group revealed regression to be rapid and in the majority of instances complete by the tenth day. No conclusive difference in relation to parity could be demonstrated. It should be pointed out that no one has yet published the definitive normal ante-partum series.

Studies of 81 women whose pregnancy was complicated by toxemia or urinary tract infection (in the broad sense of the term) revealed that in this group dilatation appeared as early as eight to twelve weeks and post-partum regression was far less frequently complete by ten days. When the infected group (twenty-six patients) were assessed separately, these differences were exaggerated. Again no conclusive difference in relation to parity could be ascertained.

The reason for this delayed regression in toxemic women is not clear. These patients represent all types of toxemia, and the type seems to have no effect on the results. Even the patients with hypertensive vascular

disease, who might perhaps be expected to approximate the normal in this respect, follow the same pattern. It is possible that these findings are related to the hormonal imbalance which has been described by the Smiths and others,¹¹ although this is ordinarily thought to be corrected by the tenth post-partum day. It would seem probable that such delayed regression with resultant stasis would be a fertile field for later urinary tract infection.

In the infected group it appears probable that infection in itself might be responsible for failure to regress, by causing scarring and infiltration of the ureteral and pelvic wall.

It would seem advisable, in view of these findings, to obtain pyelographic studies in attempting to assess patients who have had previous toxemia or urinary tract infection as a criterion of the risk involved in future pregnancies.

Conclusion

It is concluded that urinary tract infection and toxemia enhance the normal tendency to dilatation of the urinary tract in pregnancy and interfere with the usual prompt regression of these changes.

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MESONEPHROMA OF THE OVARY*

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IN 1939 Schiller¹ reported ten cases of ovarian tumors, the majority of which were cystic, in which he differentiated the tumors from the ordinary papillary types of cystic tumors. The basis for considering these tumors as a separate group was the character of the epithelial elements. These for the most part consisted of cells which lay flat upon the connective tissue stroma. The cytoplasm was scant and the nucleus lay with its long axis parallel to the connective tissue strand of the papillary projection. The cells were described as being "hob-nail" in appearance and their resemblance to endothelial cells was emphasized.

The term "mesonephroma" was suggested for the tumor because it was thought that the tumor arose from rests of embryonic mesonephron which were pinched off and retained in the subsequent developing gonad. Four reasons were advanced for this theory of the histogenesis of mesonephroma. First, that in the tumor the cells lining the cystic space are identical to the cells covering the papillary process which arrangement is typical of the glomerulus of the kidney in which the epithelium of Bowman's capsule is reflected over the capillary loops. Second, in mesonephric glomeruli the paucity of capillary loops is striking. One, two, or three vessels constitute the tuft in contrast to the many loops seen in the glomeruli of the adult kidney. Third, reconstruction by serial sections reveals the integral glomerular-like structure of the characteristic units found throughout the sections. And fourth, the intimate relationship of the mesonephron to the developing gonad in the urogenital fold of five to fifteen embryos further lends plausibility to the theory of origin.

Opposing the term "mesonephroma ovarii" Kazancigil, Laqueur, and Ladewig³ have suggested "papillo-endothelioma ovarii" reporting three cases of ovarian tumor which have identical histologic features to those described by Schiller. As a matter of fact, the authors believe the cases to be identical and this is born out by actual comparison of the photomicrographs, poor as it is for making histologic diagnoses. They considered the microscopic feature as a whole giving special stress to the endothelial-like character of the cells, the angiomatous and angio-endotheliomatous arrangement as seen in their tumors and the occurrence of a hemopoietic focus in one section. Furthermore, a reconstruction of serial sections failed to give any resemblance to glomerular-like formations.

In two papers by Jones and Seegar² and Jones and Jones,⁵ fifteen similar tumors were reported. These authors were of the opinion that the neoplasm is a distinct entity and favored the idea that the origin is epithelial rather than endothelial. They believed more proof was needed to establish the mesonephric theory of histogenesis.

In April, 1942, Schiller⁶ reported another case sent to him by Dr. Mallory. A tumor mass was present in the kidney of a 52-year-old white male. Microscopic study revealed marked similarity to previ-

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ously described ovarian neoplasms in that similar glomerulous-like units were present. In the same article Schiller raised two objections to the viewpoint of Kazaneigil, Ladewig, and Laqueur. First, that the field used for serial reconstruction contained no glomerular-like units; and second, the magnification was not high enough. Furthermore the fact that in one of their patients the tumor developed in the testicle would lend further support to the theory of mesonephric origin.

Clinically, of the ten tumors reported by Schiller seven were malignant. Eight of the ten growths presumably developed in ovarian parenchyma while in the other two, an embryoma and a dermoid contained elements highly suggestive of a mesonephroma. The ages varied from eight months to 69 years.

Of the fifteen neoplasms reported by Jones and Jones the ages varied from 40 to 72 years. Nine of the patients were dead after two and one-half years. One was alive after eleven years after extensive irradiation. In two cases in which operation alone was curative, the tumor was almost completely cystic, confined to one ovary and grossly indistinguishable from a papillary cystadenoma.

Tuta and Siebel⁴ reported a case of a 49-year-old woman who had a left ovarian cyst removed in 1933. Recurrence of a tumor in the left broad ligament recurred in 1936. The histologic sections were very similar although the sections from the latter tumor revealed no glomerular-like structures. They believed the tumor was of probable mesonephric origin.

Case Report

A white girl, 14 years of age had had some pain in the right lower quadrant of the abdomen and vomiting September 1, 1941. She had started to menstruate one year previously. The flow was irregular, rather free, with occasional clots, and was of four to six days' duration. A diagnosis of appendicitis was made by a local doctor and the appendix was removed through a McBurney incision. Healing was uneventful and the pathologist reported a normal appendix. She continued to have some abdominal cramplike pains with an exacerbation on November 1, 1941, which required hospitalization for 18 days. A diagnosis of kidney stone was made although there was no gross hematuria or stone passed. Roentgen examination of the kidney, ureter, and bladder was negative for ureteral distortion or kidney stone. Function seemed within normal limits in both kidneys. About December 25, 1941, she had an abdominal examination which revealed a grapefruit-sized mass in the left lower quadrant. At operation January 8, 1942, this was not removed because of technical difficulties and the poor general condition of the patient. A biopsy specimen was taken and a diagnosis of Wilms' tumor was made. The post-operative course was stormy, complicated by pneumonia and severe vomiting. She was in the hospital for a month, released for 10 days, and then returned because of more pain and vomiting. She was hospitalized this time for seven weeks during which time she had 10 x-ray treatments. One of us (F. H. F.) saw her at this time in consultation and made a diagnosis of malignant ovarian cyst. The lower abdomen and pelvis were filled with a firm mass, dull on percussion, and tender on deep palpation. Free fluid was demonstrable and the general picture was one of advancing malignant cachexia. Exploratory laparotomy was advised.

She entered Research and Educational Hospital April 9, 1942. Physical examination was essentially normal except for a large mass

the size of a grapefruit which was present in the lower abdomen. It was attached to the abdominal wall and was not tender. The liver and spleen were not palpable. There was an old McBurney and lower midline scar. On pelvic examination the introitus admitted one finger. The mass bulged into the vagina from the left and posterior aspects. It felt somewhat fluctuant. The cervix was visualized with a speculum and appeared normal. On rectal examination the mass filled most of the pelvis and was soft and fluctuant.

The laboratory findings were negative except for an N.P.N. of 66.7 mg. per cent, a creatinine of 4.25 mg. per cent, and a uric acid of 12.35 mg. per cent. The red blood cell count was 4.15 million on 4/9/42 and 2.9 million on 6/15/42. The white count was elevated to 15.6 thousand on 6/15/42. The roentgen examination of the abdomen revealed a soft tissue density extending from pelvis to level of third lumbar vertebra. Bones of pelvis and spine were negative.

The clinical impression was cystic ovarian tumor of questionable operability.

At operation under local anesthesia, a tumor was found to extend to the umbilicus. It was dark bluish-gray in color, and numerous adhesions between the tumor and omentum and intestinal loops made freeing and elevation of the mass impractical. Biopsy material was obtained from the tumor and from metastatic nodules in the omentum which gave the impression microscopically of a malignant granulosa cell tumor.

Seven thousand R. units were then administered and several blood transfusions were given between April 9 and July 10. The clinical course was progressively downward and she died 92 days after admission to the hospital.

At necropsy the body was extremely emaciated and there was extensive postradiation pigmentation of the skin of the lower abdomen. The abdominal cavity contained 600 c.c. of bloody fluid and filling the pelvis was a large tumor mass to which was attached a portion of the sigmoid and several loops of ileum. There were small tumor nodules over the peritoneal surfaces. A huge layer of tumor tissue lay beneath the diaphragm measuring up to 6 cm. in thickness. It obliterated the right subdiaphragmatic space completely and the left partially.

In the chest both diaphragmatic pleural surfaces were studded with tumor and the mediastinal lymph nodes contained tumor tissue. The heart was essentially unchanged. There was a single small tumor mass in the middle lobe of the right lung on the pleural surface at the junction of the lateral and interlobar surfaces. Otherwise the lungs revealed few pathologic changes except patchy atelectasis and occasional fibrous and fibrinous adhesions.

The liver with the attached tumor and portion of the diaphragm weighed 2,750 grams. There were bulging areas of tumor beneath the capsular surface of the left lobe and the cut section revealed tumor masses measuring up to 4 cm. in greatest diameter. The intervening parenchyma was of a pale pinkish-tan color consistent with fatty degeneration.

The spleen, adrenals and pancreas revealed little significant change. The left kidney weighed 80 grams and the cut surface revealed a thinning of the parenchyma and dilatation of the pelvis and calices consistent with a hydronephrosis. The right kidney was essentially normal. The left ureter was markedly dilated and the right slightly dilated.

Of the internal genitalia, only the uterus could be identified and it lay firmly attached to the anterior aspect of the tumor mass. The endometrium measured up to 2 mm. in thickness and had a smooth yellowish-gray color.

The tumor itself measured 20 cm. in diameter. It was soft to rubbery in consistency and the cut surface was of a variegated appearance. Near the lower pole it was gelatinous while near the upper aspect were varying sized areas of hemorrhage. The majority of the tumor was

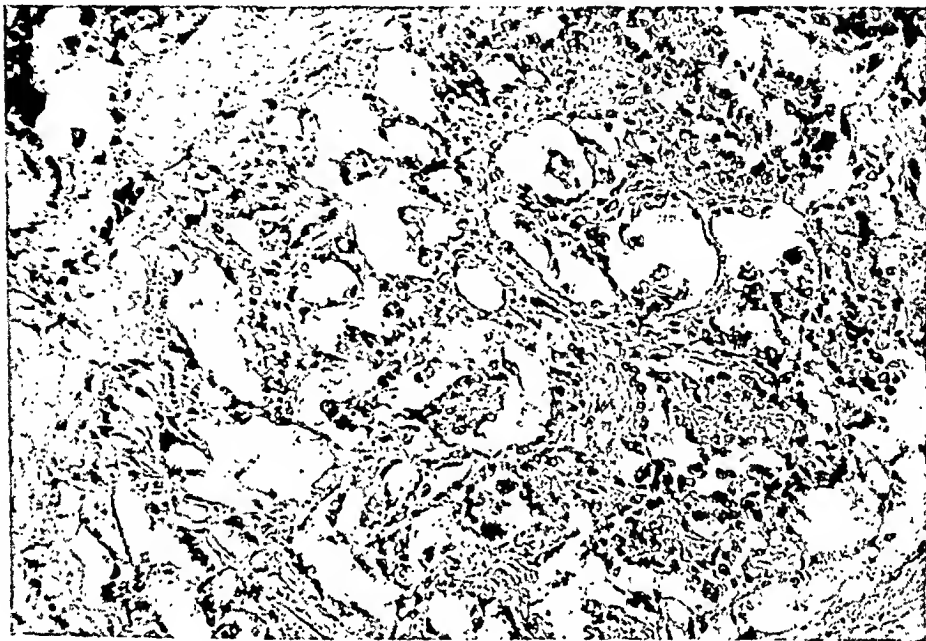


Fig. 1.—Section from tumor mass. Note cystic arrangement. (120X)

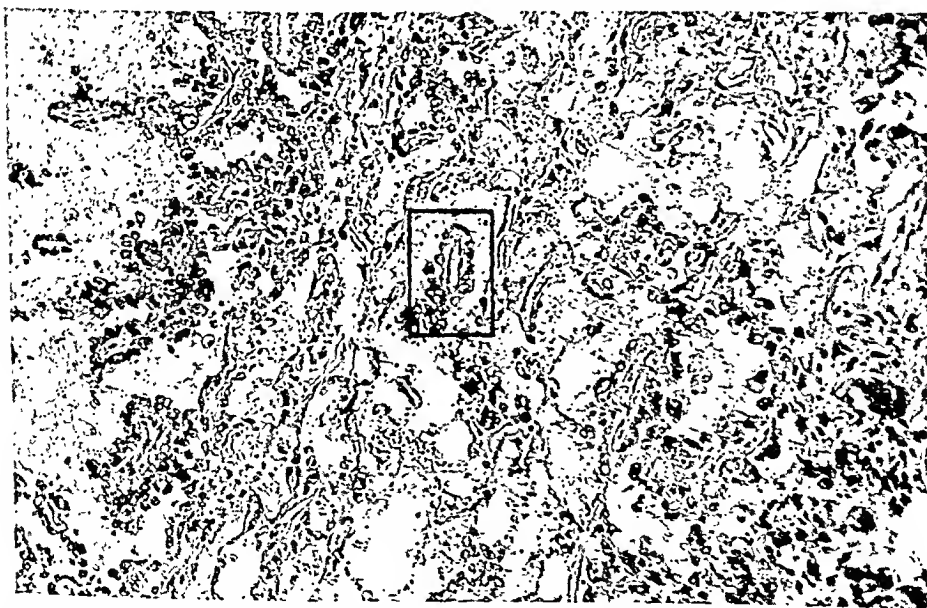


Fig. 2.—From metastasis in subphrenic space. Note individual, single capillary loops. (120X)

of a yellowish-gray color, chiefly necrotic, while near the periphery were small clusters of pearly-white tissue. Elsewhere, several cystic spaces were present which contained pulpy, reddish-tan material. No identification of ovary or tube could be made in any of the cut sections.

The metastatic lesions for the most part were of a yellowish-gray color and contained varying amounts of hemorrhage.

Microscopically the tumor was mostly necrotic, but in the viable parts there were either small cystic spaces or anastomosing trabeculae.

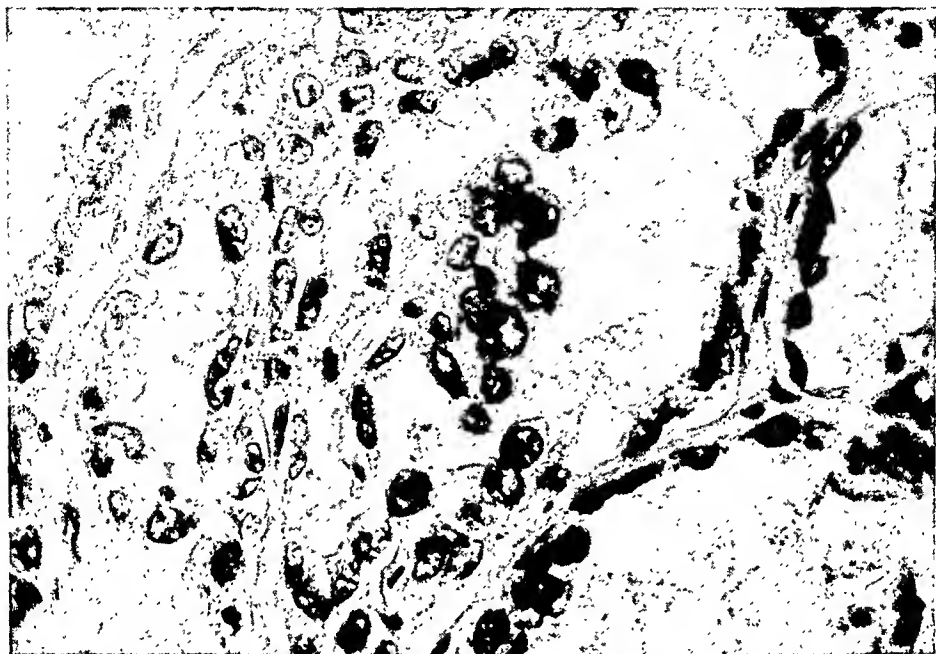


Fig. 3.—Note the scant cytoplasm, bulging nucleus, and parallelism between cells and trabeculae. (450X)

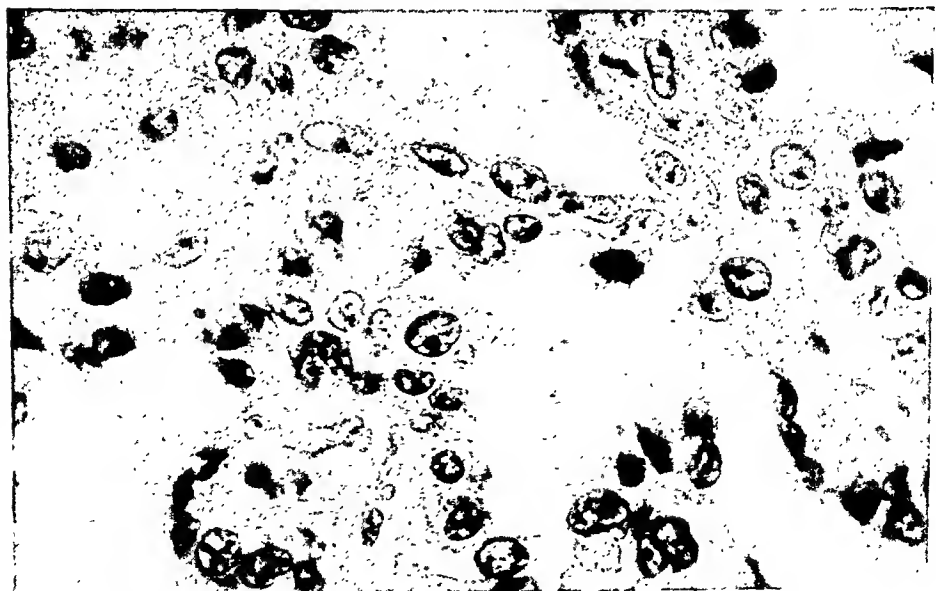


Fig. 4.—Note endothelial-like appearance of the cells, also mitotic figures. (450X)

In some areas proliferation of the cells resulted in solidly packed areas of tumor cells. Figs. 1 and 2 typify the cystic and trabecular arrangement. It will be noticed that in the cystic spaces for the most part only a single loop fills the space. In Fig. 2 in the central part of the field, a single loop is shown extending from one side of a complete cystic space. In other areas the continuity is broken and only a single tuft is seen lying within the space.

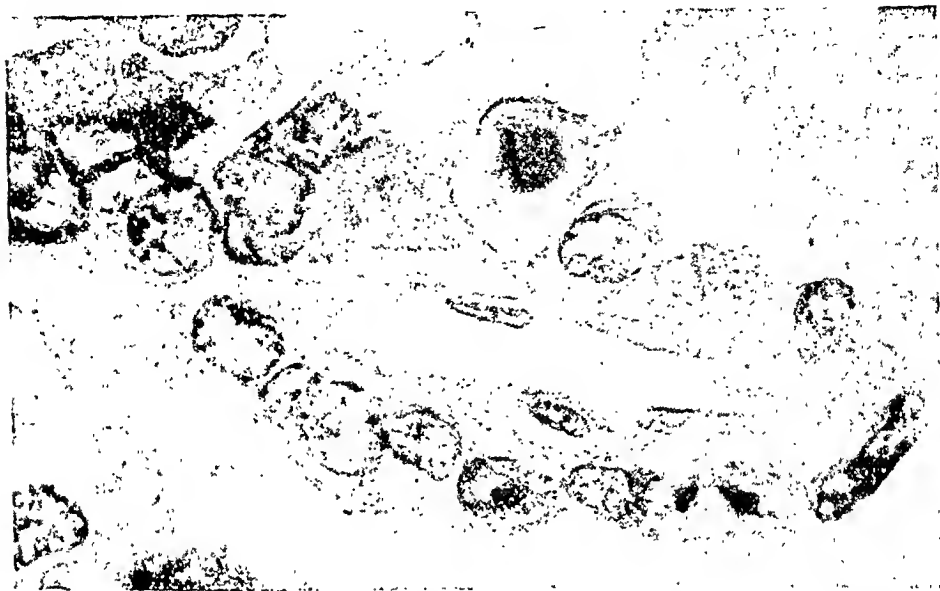


Fig. 5.—Central part of Fig. 2. Note cellular characteristics, integral relationship but definite difference between tumor cells and endothelium of the blood vessels. (950X)

Under higher magnification as seen in Figs. 3 and 4, the actual cellular characteristics are evident. The cells highly resemble endothelium; the long axis of the cell is parallel to the connective tissue trabeculae; the cytoplasm is quite scant while the nucleus bulges, is vesicular, and has a well-defined nucleolus. In Fig. 4, mitotic figures are plainly seen. Fig. 5 is a higher magnification of the central portion of Fig. 2. It brings out the histologic features of the cells more sharply, but mainly it shows the distinct separation between the layer of tumor cells and the thin walled vessel forming the tuft.

A phosphotungstic acid stain revealed the cellular detail more clearly and served to show the difference between the tumor cells and endothelial cells of the blood vessel, while a muci carmine stain was only of negative value in that no mucin was found.

The stroma was either necrotic or composed of trabeculae separating the clusters of cystlike spaces. It was made up of a loose network of pink staining fibrils, and numerous elongated spindle-shaped nuclei resembling nuclei of fibrocytes were present (Fig. 1). In some sections there were huge extravasations of red blood cells, while fewer numbers of red blood cells were found in the cystic spaces as well.

Discussion

Since the first report of this particular type of ovarian tumor, a total of approximately 27 cases have been recorded. The striking similarity of the microscopic features of this tumor is sufficient to justify con-

sidering it as belonging to the group of previously reported cases. But then there arises the problem of nomenclature and histogenesis. The term mesonephroma as submitted by Schiller aptly catalogues this entity and the arguments for its histogenesis are convincing. Papillo-endothelioma is a good descriptive term but stops short at just that. Furthermore, there is much uncertainty as to whether the tumor can be justly called an endothelioma. The appearance is unlike any other described endothelioma occurring extragenitally. If the tumor were endotheliomatous, occurrence in other sites should be expected. Furthermore, there is a distinct separation between the blood vessels and the actual tumor cells as seen in the higher power photomicrographs. The endothelial lining of the blood vessels is quite distinct and histologically different from the tumor cells surrounding the loop. Lastly, since a diagnosis of endothelioma cannot be made in view of insufficient evidence based only on superficial resemblance to endothelium, it is better to create a distinct entity from other forms of ovarian tumors with dissimilar histologic structure. On the other hand, it will be difficult to prove conclusively the mesonephric origin of this tumor. Multiple serial sections should afford a method in which the integral glomerular-like structure is shown to be the basic unit. Furthermore, it is to be hoped that a provocative investigation of previous ovarian tumors as well as a study of other sites of tumors to determine possible extragenital foci, will result in other case reports to definitely establish mesonephroma as a distinct ovarian tumor.

From the clinical standpoint several factors must be mentioned. First, this tumor can occur at any age. Second, the tumor does not have abnormal hormonal activity and does not cause feminizing or masculinizing symptoms. Third, the obvious malignant character of the neoplasm in this case further supports the impression of the tendency in this direction seen in previously reported cases. The lack of response to deep x-ray irradiation in this case emphasizes the need of early clinical recognition and complete surgical removal. Grossly the nature of the tumor may be suspected but the diagnosis will probably always depend upon microscopic study. In all cases a total removal of both uterus and adnexa and follow-up treatment with x-ray about 10,000 R. units is indicated.

Summary

A case of ovarian tumor which microscopically corresponds to "Mesonephroma Ovarii" has been presented. The literature has been reviewed and the arguments for the histogenesis have been mentioned. It is felt that the evidence and arguments favor considering the tumor as an entity and that the term "mesonephroma" should be accepted at least until more evidence, pro or con, is forthcoming. The clinical features have been listed.

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THE PSYCHOSOMATIC TREATMENT OF FUNCTIONAL DYSMENORRHEA BY HYPNOSIS

A Preliminary Report

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THE treatment of functional dysmenorrhea is still in a relatively unsatisfactory stage. Considerable effort has been expended in obtaining results not only with analgesics and sedatives but also with expensive endocrine preparations. None has proved exceptionally successful, but a wide variety of these preparations have been reported to yield relief in some patients.

It is acknowledged by many investigators, that the relief from painful menstruation may often be the result of unintended suggestion derived from the therapy, regardless of what preparations are used. Such results are in agreement with the theory held by many, that there is a definite psychic factor associated with functional dysmenorrhea, and the principal feature of this is a lowered threshold to pain. Thus, contractions of the uterus are conveyed to the consciousness of the individual, whereas normally these contractions are not registered as pain. In some patients this lowered threshold to pain may be due to an underlying psychosomatic condition.

It is claimed by a number of competent investigators,¹⁻³ that functional dysmenorrhea never occurs without previous ovulation indicating that these patients have normally functioning ovaries. The most successful attempts to treat this condition with endocrine substances seem to occur where ovulation has been suppressed.^{4, 5} It may be questioned, therefore, whether such therapy is desirable, where an abnormal functioning of the ovaries is induced in order to correct a condition associated with normal ovarian activity. A more rational approach seems to be indicated in treating dysmenorrhea by attempting to raise the pain threshold, or in some other way, block the sensory pathway to the higher centers of the brain.

Since relatively weak suggestion has been partially effective in bringing relief, a type of psychotherapy, combining the use of more effective suggestion as the main implement, would seem desirable for treating this condition. Such a mechanism where powerful suggestion can be transmitted is available in the form of hypnosis as scientifically used in medicine today. The use of hypnosis in ameliorating many subjective sensations of an unpleasant nature has been shown for many years to be an effective and harmless form of therapy. At present, hypnosis is being used extensively abroad for the treatment of many functional diseases associated with wartime conditions, such as bomb

shock and other war neuroses. Unfortunately, the preponderance of scientific work today in the field of hypnosis is being done by psychologists and is chiefly confined to nonclinical investigation. Furthermore, there are considerable skepticism and prejudice, by the laity, against hypnosis.

Certain functional disorders, especially in gynecology and obstetrics, lend themselves remarkably well to this form of therapy and should command the attention of the clinician. Because many of the successful results in treating functional dysmenorrhea are on the basis of suggestion, we have selected this condition for the possibility of demonstrating relief through hypnotism, by means of which powerful and concentrated suggestion may be easily applied. We wish to emphasize that hypnosis is only a means toward treatment, and when combined with modern psychoanalytical skill and knowledge it can be a much more effective treatment of functional dysmenorrhea than any of the methods in use today. Diek,⁶ Bramwell,⁷ and other investigators have reported results similar to ours, so such experiments are by no means original except for a difference in technique. This report is presented merely to acquaint American physicians with the promising field available for such a type of therapy.

Methods and Results

Cases Treated by Hypnosis and Posthypnotic Suggestion

The following procedure was used in four cases: after rapport is established with the patient, hypnosis is induced. This is characterized by a state of generalized hypersuggestibility which is about twice that of the normal waking state. The technique and the various states of hypnosis have been described by Erickson,⁸⁻⁹ Bramwell¹⁰ and Schilder and Kanders.¹¹ Young¹²⁻¹⁴ has published several excellent reviews of the literature on hypnosis and suggestion. Nearly all investigators concur that suggestions are more effective when the patient is in a deep somnambulistic state. Suggestions are made in this state that the next menses may be free from pain or without excessive discomfort. Also suggestions are made that the next menses will be normal in all respects. Posthypnotic suggestions last about a month, and when repeated the desired effect may become permanent, as has been previously pointed out by Kellogg¹⁵ and Patten.¹⁶ These suggestions are, as Erickson¹⁷ has described, separate hypnotic states, arising spontaneously in the individual. All four cases were permanently cured using this method. Only one treatment was necessary to bring permanent relief in two cases. Three to twelve treatments were necessary for the other two cases.

The following case histories are typical of the methods and results.

CASE 1.—Miss L. S., aged 17, had painful menses since the age of nine and a half. The menses were always irregular. She was forced to retire to bed for 24 to 36 hours after the onset of the pain which usually occurred about 12 hours after the period began. It consisted of acute lower abdominal cramps accompanied by considerable nervousness, nausea and tension. She had received extensive therapy includ-

ing dilatation and curettage, analgesics and endocrine preparations. A presacral sympathectomy was being considered, to which she had agreed.

On August 2, 1941, deep hypnosis was easily induced. Suggestions were given to the effect that her next menses would be free from discomfort; that every night before going to sleep she would say to herself, "I will have no pain. I have no dread and anticipation for my next period." These suggestions under hypnosis were repeated seven times between August 2, 1941 and August 29, 1941. The period began on September 6, 1941 and was remarkably free from pain although there were slight cramps. She did not have to go to bed. After four hypnotic treatments at weekly intervals, using the same suggestions, her next menses on October 11, was entirely normal in every respect. For one year, without any further treatments, she has been free from pain, nervousness and all menstrual discomfort. In addition her periods have been regular.

CASE 2.—Miss D. K., aged 19, had severe dysmenorrhea of three years' duration. It consisted of severe lower abdominal cramps accompanied by depression. The menses usually lasted for four days during which time she was unable to work.

The patient had consulted several physicians and had tried all kinds of hypodermic treatments and drugs with little or no results. On November 15, 1941, deep hypnosis was induced easily. The same suggestions were given as in Case 1. The patient was hypnotized at weekly intervals twice before her next period. On December 6, the menses were entirely normal. All menstrual periods have been normal since that time. She has been relieved of her depression entirely and can now even practice aerobic dancing during her entire menstrual period.

Cases Treated by Hypno-Analysis and Age Regression

It occurred to us that some cases of functional dysmenorrhea present a characteristic constitutional psychosomatic pattern which may be responsible for a lowered pain threshold. Because latent psychogenic factors contribute to the intensity and production of the dysmenorrhea, they must be determined by an exhaustive study of the personality. We have utilized age regression with hypno-analysis, which is a rapid form of psychoanalysis under hypnosis, in five cases. This technique of hypno-analysis has been described by Hadfield,¹⁸ Karup,¹⁹ and Taylor.²⁰ The patient is regressed to a preadolescent age following the method described by Platonow²¹ or reverted to the age prior to the onset of the dysmenorrhea. The patient is then slowly reoriented to the present chronological age. The development of emotional conflicts, personality changes, inhibitions or harmful habit patterns can be discovered. Appropriate suggestions are then made toward their removal. After the patient's consciousness is re-educated by intensive psychotherapy under hypnosis, a cure may be effected readily. A total amnesia for the entire menstrual period may be produced in some individuals.

However, it must be emphasized that hypnosis when used in these cases is only the means toward treatment, not the cure itself. It effectively speeds up the entire analytical process. The use of hypno-analysis and age regression readily extracts intimate facts held in the

subconscious mind which ordinarily would not be available to the physician with the patient in the wakened state.

Five patients were regressed using this method. Two patients had never experienced orgasms. One patient, whose case is described below, had no improvement because of the husband's sexual impotence and premature ejaculation. However, the husband in spite of treatment never was able to have satisfactory intercourse with his wife. The other patient had complete relief from menstrual discomfort after attaining orgasms following suitable conditioning while in the hypnotic state. Her husband was normal sexually. One patient was a habitual masturbator who had complete recovery after adequate sexual advice was given. One had dysmenorrhea only during two unhappy marriages and between these marriages she had no dysmenorrhea. This patient was only partially improved since she is still unhappily married to her second husband. One woman had dysmenorrhea only after excessive sexual excitement without intercourse. Marriage was advised in this case. Shortly after the patient followed our advice and married, the painful periods ceased.

The following case histories are typical of the methods and results.

CASE 1.—Mrs. R. B., aged 31. Para ii, married eleven years. Severe dysmenorrhea began immediately after marriage. Cramps preceded onset of flow and became more severe as bleeding ensued accompanied by headache and nervousness. She was hypnotized easily on March 6, 1941. Suggestions were given at weekly intervals as in the cases previously described. The next menses on April 2, was unimproved. Four applications of hypnosis at weekly intervals were made prior to onset of period on May 1, with only slight improvement. On May 7, she was regressed to the age of 18 and gradually reoriented to the present age. The following facts were elicited. She had never had an orgasm while married even though her husband was potent sexually. She abhorred coitus and considered it "something to be endured." Following the birth of her second child three years ago her libido was lost completely. Her husband threatened a divorce. The patient professes some love for her husband and a desire to at least satisfy him. One week later under hypnosis, suggestions were given to the effect that she would have an orgasm the next time she had intercourse. Since she had experienced orgasms before her marriage there was no need to describe the subjective sensations. These suggestions were repeated at three weekly intervals during which time she abstained from intercourse. Coitus occurred on June 10, and although not accompanied by an orgasm the patient stated "she almost felt one." Her husband was told to have intercourse on June 14, and he was given proper sexual advice. This advice was followed and the patient experienced an orgasm. Her sexual life has been satisfactory since then and all menstrual discomfort disappeared completely.

CASE 2.—Mrs. L. F., aged 20, had painful periods for the past two years. Extreme nervousness was present during the entire period. For the past year her menses have been most irregular. Patient states, "she began to have menstrual cramps at the age of 18." All therapy

was of no avail. Pain began on the first day and was present on the second and fifth days. She was hypnotized on October 4, 1941 and was regressed to the age of 17 where the following facts were elicited. Her menses first became painful after meeting her husband whom she never loved. She had never achieved an orgasm with her husband during intercourse although this occurred during preliminary love-making. Her husband was inadequate sexually. She was given posthypnotic suggestions to the effect that she would have an orgasm during intercourse and her menses would be painless. On October 11, the suggestions under hypnosis were repeated. On October 17, the menses were free from discomfort until the fifth day. Orgasms were not achieved. The next menses was on December 7, 1941, and was painful and the patient failed to return for further treatment.

Discussion

In this small series of nine cases treated as described above, the results are most gratifying. All the patients were referred by competent gynecologists. No obvious cause for the cyclic pain could be demonstrated in any of the cases. Various therapeutic procedures had been tried on each patient with disappointing results.

The inconvenience of using hypnosis is relatively negligible when compared with symptomatic therapy and the expense of multiple injections required for much of the endocrine treatment. The technique described here can easily be acquired by any physician. In addition, temporary dysfunction of the ovaries is not induced and the cures are relatively complete and permanent. Through hypnosis, underlying psychosomatic factors may be discovered and effectively removed, thereby raising the threshold to pain. Again through hypnosis and posthypnotic suggestion a block may be established in the nervous pathway between the uterus and the pain center in the hypothalamus. Kuntz²² has described this nerve pathway. One of the explanations for this block may be that hypnosis is "synaptic ablation." Hull²³ states, "through hypnotism one may have an effective control of the higher centers and certain autonomic processes only feebly influenced by voluntary effort. There are additional possibilities that the ready control of such physiological mechanisms might prove of practical value in the treatment of numerous somatic disorders." Evidence which demonstrates the mechanism of hypnosis in these conditions would probably require a more fundamental type of investigation. From a practical standpoint however, hypnosis offers a valuable method to our therapeutic armamentarium in giving relief to a group of patients who suffer considerably at regular intervals. This fact alone warrants extensive trial with hypnosis. Hypno-analysis and age regression elicit latent psychogenic factors from the subconscious mind which usually are responsible for the dysmenorrhea. In addition, the patient may be unaware of these or have no desire to tell them to the physician. In several articles the brilliant work of Erickson,^{24, 25} comprising thousands of cases, has shown that in competent hands there

should be no untoward reactions or risk following the use of hypnosis. The prejudice which has relegated hypnotism to obscurity as an unexplained medical phenomenon, and which may have been warranted years ago because of unscientific and unscrupulous activities, should now be abolished, and an objective evaluation placed on the use of this valuable form of treatment. In addition through quantitative and controlled experiments that were not available to the earlier investigators, much more can be learned regarding its practical therapeutic application.

Summary

Seven of nine patients with functional dysmenorrhea, who obtained little or no relief following a wide variety of symptomatic and endocrine therapy, were completely relieved of their menstrual cramps and discomfort following the use of hypnosis either by itself or with hypnoanalysis and age regression. One was partially relieved and the one failure is ascribed to factors beyond our control.

This form of psychotherapy, which acts by raising the pain threshold directly or through the eliciting of psychogenic factors indirectly causing the pain, is a convenient and effective therapeutic procedure for permanently curing this ordinarily refractory condition.

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ORAL HORMONAL TREATMENT OF FUNCTIONAL AMENORRHEA

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THE treatment of functional amenorrhea poses an interesting problem to the physician. Great strides have been made in the management of these cases during the past two decades, but the final step, the resumption of spontaneous menstruation, often eludes us.

The causes of functional amenorrhea are manifold; consequently, a host of therapeutic regimens are employed to cope with this menstrual derangement. The control of obesity in the stout individual, psychiatric therapy of the mental cases, an adequate nutritional regimen in the undernourished and thyroid medication for the myxedematous patient have all been successfully employed in the treatment of amenorrhea.

The problem is further complicated by the spontaneous resumption of menstruation. This phenomenon makes it difficult to evaluate properly any method of treatment. Furthermore, amenorrheic women have been known to ovulate and become pregnant without having had any recent menstruations.¹ Treatment must be individualized and may be instituted only after a careful diagnostic survey has been completed.

The most satisfactory hormonal approach to this problem has been the use of the estrogens,² progestogens,³ or a combination of the two.⁴ Estrogenic therapy has not been as uniformly successful as the use of progestogenic hormone alone or in combination with the estrogens.⁵ The majority of investigators has not found the gonadotropic hormones effective in this field but there have been occasional reports of their successful use.⁶ None of these methods has brought about the resumption of spontaneous menstruation over any considerable length of time.

The roentgen ray⁷ and the surgeon's scalpel⁸ have also been employed to treat functional amenorrhea. In the light of mature judgment neither of these methods can be recommended.

Hormonal therapy has enabled us to produce bleedings almost at will, although they are not true menstruations.⁹ This is a definite step forward. The effect of a uterine bleeding on a woman who has despaired of ever resuming menstruation is not to be underestimated. The psychic stimulus of the bleeding often enables her to maintain self-esteem and enhances her ability to meet the problems of life.

It has been demonstrated previously that all primary amenorrhea cases require a preliminary course of estrogenic medication to obtain bleeding by the use of progestogenic hormone. Cases of secondary amenorrhea will bleed without priming with estrogens only if the last spontaneous period has occurred no longer than two years ago.³

We are presenting a series of 18 patients—5 cases of primary and 13 of secondary amenorrhea—in whom with one exception, a careful diagnostic survey failed to reveal any definite causes of the amenorrhea. This one woman probably had a surgical castration although the operative record is not clear on this point. The survey of all patients included complete physical examinations, visual field determinations, routine urine analysis, blood counts, sugar tolerance tests, basal metabolic determinations, endometrial studies whenever feasible and occasionally determinations of the excretion rate of estrogens and gonadotropins in the urine. Consequently, we consider these problems as belonging to the functional amenorrhea classification—with the exception of the one case mentioned above.

In all patients, regardless of the duration of their amenorrhea, treatment was instituted with estrogenic hormone followed by progestogenic medication.

In our preliminary experiments estrogenic hormone was administered parenterally; later on we changed to oral estrogenic medication. The progestogenic hormone was always given by mouth, in an attempt to free the patient from the necessity of hypodermic medication. It is our contention that these patients do better if they are not required to visit the clinic or their personal physician at frequent intervals.

Method and Results

The parenteral estrogenic medication, first employed, was given as a series of five daily intramuscular injections of estradiol benzoate, 0.33 mg. each. This was followed immediately by five daily doses of 60 to 80 mg. of pregnenolone by mouth. The use of 60 mg. of pregnenolone was as satisfactory as the higher doses of this progestogen. When the estrogens were employed orally, stilbestrol was given for five to ten days in doses varying from 1 to 3 mg. daily. The most satisfactory regimen was to give 2 mg. of stilbestrol daily for five days. This, too, was followed by five daily doses of 60 mg. of pregnenolone.

Several consecutive courses, at monthly intervals, were given to each patient of our group. As indicated in Table I, a total of 62 courses of treatment, given to 18 women, resulted in 55 bleedings. Thus, there were about 10 per cent failures. The ratio of failures was almost the same regardless of whether estradiol benzoate or stilbestrol was employed for priming the patients.

Five of the 18 patients menstruated regularly after their courses of therapy were completed. These women were young, their average age being 22. It was noticeable that they all were slim, extremely feminine individuals, completely free of all endocrine stigmata. The average duration of the amenorrhea previous to therapy of four of these cases was eleven months. The fifth, an older woman, aged 34, had been without periods for two years. There were no cases of primary amenorrhea among the women who went on to menstruate regularly.

Three other women in our series had several menstrual periods after their treatment had been completed, but they soon ceased to bleed. They are not included in the five women who are now menstruating regularly. The longest period of observation of the regularly menstruating women is 14 months; the shortest is four months.

The endometrial findings are of interest. We obtained two specimens of the endometrium from each of twelve of our patients. All showed the absence of secretory endometrium before treatment. The post-medication specimens of three patients exhibited secretory changes but these were all of the mixed variety. These three patients went on to menstruate regularly after their treatments were completed. However, we were unable to obtain a third specimen of the endometrium after they had resumed their regular menses. From the two other patients in whom several courses of therapy elicited regular bleedings, no biopsies were obtainable. In six instances of our series, the biopsy specimens after therapy showed proliferation, in three there was atrophy of the endometrium.

TABLE I. SUMMARY OF TREATMENT AND RESULTS

NAME	AGE	NO. OF PREGNENINOLONE AND ESTRADIOL BENZOATE COURSES	NO. OF PREGNENINOLONE AND STILBESTROL COURSES	NO. OF BLEEDINGS	PER CENT SUCCESSSES	SUBSEQUENT SPONTANEOUS MENSTRUATIONS	ENDOMETRIAL BIOPSY AFTER MEDICATION
SZ*†	19	3	2	4	80	14	----
JS‡	26	2	0	2	100	0	Proliferative
BC§	18	3	1	2	50	0	----
HG	18	0	2	2	100	2	----
SK	25	1	2	3	100	0	Proliferative
TH¶	20	3	5	8	100	Cont. therapy	Proliferative
RF	28	0	3	3	100	0	Proliferative
MM†	23	3	0	3	100	12	Mixed
JC¶	26	0	5	4	80	0	Proliferative
SL†	19	0	3	3	100	8	----
LB¶	27	0	3	3	100	0	Atrophic
KO†	34	0	2	2	100	4	Mixed
RE¶	33	0	3	2	66	0	Atrophic
RDeK†	17	0	4	4	100	4	Mixed
MJ	17	0	3	3	100	1	----
SP	31	0	3	2	66	1	Atrophic
BC¶	34	0	3	2	66	0	Proliferative
CL	17	0	3	3	100	0	----

* Began to menstruate during third stilbestrol course.

† Menstruates spontaneously up to date.

‡ Surgical castration.

§ One failure with each type of course.

¶ Primary amenorrhea.

Summary

1. It is possible to cause uterine bleedings in functional amenorrhea by the use of orally effective estrogenic and progestogenic preparations. There are 10 per cent failures by this method.

2. Primary and secondary amenorrhea respond equally well.

3. Production of bleedings can be repeated as often as is desired.

4. They will be obtained from any type of endometrium, usually from a proliferative one.

5. Approximately 41 per cent of the women with secondary amenorrhea continue to menstruate regularly following several courses of treatment. The parenteral use of the estrogens and progestin has resulted in the spontaneous resumption of vaginal bleedings in only a few isolated cases. We are unable to explain the difference in the end results between these two methods of administering the hormones.

6. The women who achieved regular menstrual bleedings were young, slim, very feminine and without endocrine stigmata. There were no primary amenorrhea cases which continued to bleed after cessation of therapy.

7. Regular menstruation is more likely to follow if the endometrium shows some evidence of the secretory phase.

8. The most practical plan for treatment consists in the oral administration of 1 mg. of stilbestrol, twice a day, for five days; this is immediately followed by 60 mg. of pregnenolone daily for five days. The entire course of medication should be repeated at least three times to secure the best end results.

The author desires to acknowledge his indebtedness to Dr. Maurice Rashbaum and Dr. Edward A. Horowitz for permission to incorporate four of their cases in this series.

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STUDIES ON THE RH FACTOR*

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RECENT studies by Levine and his co-workers¹⁻⁶ have shown the importance of iso-immunization of the Rh- mother by Rh+ fetal blood. This work has been confirmed by others.⁷⁻¹⁰ Before proceeding with the present report, it may be well to récall some fundamental points about the Rh factor. Rh is an agglutinin present in the human erythrocyte, and was described first by Landsteiner and Wiener¹¹ with the aid of rabbit antirhesus blood immune sera.† It is so named because of its relationship to a factor in the blood of the Rhesus monkey. Approximately 85 per cent of the random human population possess the Rh agglutinin in their erythrocytes, and their blood is known as Rh+. Approximately 15 per cent of the population do not have the Rh agglutinin in their erythrocytes, such bloods being termed Rh-. If the Rh agglutinin is repeatedly introduced into the blood stream of an Rh- individual, it acts as an antigen and causes the production of anti-Rh agglutinin.^{2-14, 7, 10} This process is termed immunization, or better, iso-immunization, since both the antigen (Rh) and antibody (anti-Rh) belong to the same species.

If an Rh- individual receives blood transfusions from Rh+ donors, there will be no reaction after a variable number of transfusions, but the recipient may develop, sooner or later, anti-Rh agglutinins as a result of iso-immunization. If the recipient, thus immunized, should receive a transfusion of Rh+ blood, there will be a severe, if not fatal, transfusion reaction due to the hemolysis produced by the action of the anti-Rh agglutinins on the Rh+ transfused blood. Similarly, an Rh- mother who bears an Rh+ fetus may become immunized. In such cases, the Rh+ fetal erythrocytes must enter the maternal circulation, and act as an antigen, so that the mother may develop anti-Rh agglutinins. These anti-Rh agglutinins then pass the placental barrier, enter the fetal circulation, and hemolyze the fetal red blood cells. The result is the disease entity known as erythroblastosis fetalis.²⁻⁵ An Rh- mother thus iso-immunized by an Rh+ fetus should not receive a transfusion with Rh+ blood, because of the almost certain liability of a severe transfusion reaction.

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Studies on Iso-Immunization at Bellevue Hospital

At Bellevue Hospital in 1937, a patient with mild pre-eclampsia was delivered of a badly macerated fetus. Because of intrapartum and postpartum hemorrhage she received a blood transfusion soon after delivery. Her husband was the donor. Both donor and recipient were in group O. The transfusion was promptly followed by a very severe reaction resulting in jaundice and anuria. The patient's blood was studied by Levine and Stetson,¹⁵ who found that it contained an atypical agglutinin which agglutinated about 80 per cent of group O bloods. She was then transfused several times with compatible blood and ultimately recovered. The atypical agglutinin gradually disappeared from her blood and was entirely absent by the end of one year. The deduction could thus be drawn by Levine and Stetson that the pregnancy caused iso-immunization in the mother—in other words, that the fetal blood or some other product of gestation induced the production of atypical agglutinins in the mother. Following the discovery of the Rh agglutino-gen by Landsteiner and Wiener, the patient's blood was found by Levine and Katzin to be Rh-, and her husband's Rh+. The compatible donors successfully used for subsequent uneventful transfusions were later found to be Rh-. It was then concluded that an Rh+ fetus induced the production of anti-Rh agglutinins in the Rh- mother. This case served to stimulate further study of iso-immunization in pregnancy.*

In order to obtain more information about the occurrence of anti-Rh agglutinins, patients on the obstetric service of Bellevue Hospital were studied beginning in September, 1940, and continuing for a period of 6 months. During this time the sera of 114 selected obstetric patients were examined for the presence of anti-Rh agglutinins. Patients were selected so as to include all types of obstetric complications such as pre-eclampsia, placenta previa, premature separation of the normally implanted placenta, amniotic sac infections, prematurity, and immaturity of the infant, intrauterine death of the fetus occurring well in advance of labor, etc. In addition, many entirely normal cases were investigated. The blood was collected intrapartum and at various times in the puerperium. There were 7 mothers in the series who delivered macerated fetuses, but, from the clinical history, in only 2 cases did erythroblastosis fetalis appear to be the probable cause of the intrauterine death. There were no definite cases of erythroblastosis fetalis during this period of the study.

At this time it was thought that possibly a retained placenta or macerated fetus served as the antigen which caused the production of anti-Rh agglutinins in the mother. The true explanation of the pathogenesis of erythroblastosis fetalis had not been evolved. In not a single

*It is now established that the factor studied by Levine and Stetson in 1937 to 1939 was Rh and the agglutinin was anti-Rh in specificity.⁵

instance of the 114 sera studied were anti-Rh agglutinins demonstrable. Unfortunately, during this period it was not possible to determine whether or not the mother was Rh positive, since potent human anti-Rh sera suitable for diagnostic purposes were not yet available.

The conclusions to be drawn from the above results were chiefly of a negative nature. One could definitely say that anti-Rh agglutinins were not demonstrable in the sera of the great majority of obstetric patients. Subsequent work by Levine and co-workers,⁵ however, showed that 50 per cent of Rh- mothers of erythroblastic infants did not have anti-Rh agglutinins in their serum. Nevertheless, iso-immunization must have occurred since it has been found that this group of mothers are just as subject to intragroup transfusion accidents as are the mothers with anti-Rh agglutinins.

Beginning in February, 1941, and continuing for a period of 16 months, the bloods of selected patients were studied to determine whether they were Rh+ or Rh-. Potent anti-Rh agglutinins derived from mothers of erythroblastic infants now had become available. All sera were also tested for the presence of anti-Rh or other atypical agglutinins. An attempt was made to examine the blood of each mother who had an unexplained stillbirth or neonatal death and of some mothers with various complications of pregnancy. Unfortunately, circumstances prevented the inclusion of every mother with a stillbirth or neonatal death. It is felt, however, that the maternal blood was examined in every case where the diagnosis of erythroblastosis fetalis was at all likely. A total of 99 cases was thus investigated out of slightly more than 2,000 deliveries.

Cases of Erythroblastosis Fetalis

During this period of study there was noted a total of 7 stillbirths or neonatal deaths in which the diagnosis of erythroblastosis appears definite. One patient delivered two of these stillbirths. Short summaries of these cases follow:

CASE 1.—H. P. was a diabetic, para ii, gravida iii. The first two children were alive and well, the youngest being 8 years of age. The present pregnancy resulted in the easy delivery, as an assisted breech, of a 6-pound infant. The baby was pale at birth and became jaundiced on the following day. Shortly after this the infant died. Post-mortem examination corroborated the clinical diagnosis of erythroblastosis fetalis. The blood of the mother was Rh- but no anti-Rh agglutinins were demonstrable in the maternal serum.

CASE 2.—E. M., para ii, gravida iii. The first two children were alive and well, both weighing over 9 pounds. At the end of her third pregnancy she was delivered spontaneously of a macerated fetus weighing 9 pounds 14 ounces. The placenta was thick, edematous, and suggestive of erythroblastosis fetalis. Due to maceration the post-mortem examination failed to yield definite information. The mother's blood was Rh- and contained potent anti-Rh agglutinins.

CASE 3.—S. J., para iii, gravida iv. Although the first infant is alive and well, it was jaundiced at birth. The next two pregnancies resulted in macerated stillbirths. The fourth pregnancy resulted in a macerated immature stillbirth weighing 2 pounds. The blood of the mother was Rh- but no anti-Rh agglutinins were demonstrable in her serum. The father was found to have Rh+ blood.

CASE 4.—J. O., para ii, gravida iv. The first two infants were stillbirths. Their conditions at birth were not known. The third pregnancy terminated in a spontaneous abortion at 3 months. The fourth pregnancy terminated in a spontaneous delivery of a 7-pound 6-ounce macerated infant with an enlarged liver and spleen. The blood of the mother was Rh-, that of the father, Rh+.

CASE 5.—P. T., para ii, gravida iv. The first pregnancy resulted in the delivery of an apparently normal infant which is now alive and well at the age of 18. Then came a premature stillbirth, followed by a late abortion. The present pregnancy resulted in a spontaneous delivery of a very pale, 7-pound stillborn fetus, which was not macerated. The spleen and liver were definitely enlarged clinically. Permission for post mortem was not obtained. The maternal blood was Rh-, but no anti-Rh agglutinins were demonstrable in the serum. The paternal blood could not be obtained for examination.

CASES 6 AND 7.—B. A., para vi, gravida viii. The first infant was normal at birth and is alive and well. The following pregnancy ended in an abortion. The next 2 pregnancies each resulted in the delivery of a term infant which was jaundiced at birth and died after a few days. The fifth pregnancy ended with the delivery of an apparently normal term infant, who is alive and well. During the sixth pregnancy this patient was cared for at Bellevue Hospital for the first time. It terminated in the birth of a 3-pound macerated infant. During her last two pregnancies this patient returned to Bellevue Hospital for care. Both are included in this study. The seventh pregnancy terminated in the delivery by version and breech extraction of a markedly macerated 1-pound 3-ounce fetus presenting by the shoulder. There was moderate intra-partum bleeding due to premature separation of a normally implanted placenta. The blood of the mother was Rh- and her serum contained moderately active anti-Rh agglutinins.

Eleven months later the same patient was delivered spontaneously of a macerated stillbirth, weighing 1 pound 1 ounce. Because of post-partum hemorrhage a blood transfusion was started. The patient experienced a severe chill after approximately 25 c.c. of blood had run in, and the transfusion was discontinued promptly. The blood had been cross-matched carefully but had not been incubated, as advised by Levine.⁴ Her puerperium was uneventful. While her blood was Rh-, no anti-Rh agglutinins were demonstrable in her serum.

This patient is one of the few whose blood has been studied for the Rh factor in 2 successive pregnancies. While certainly both fetuses died in utero because of erythroblastosis fetalis, anti-Rh agglutinins were demonstrable in the maternal serum following the first pregnancy but were not found after the second. Since the patient had an intra-group transfusion reaction from only 25 c.c. of blood, it would appear most probable that anti-Rh agglutinins were fixed to the cells of the reticulo-endothelial system although not demonstrable in the serum.^{4, 13}

It is assumed that the fixed tissue agglutinins are capable of destroying transfused Rh+ blood. Accordingly, all Rh- patients should receive blood from Rh- donors, even though cross-matching with Rh+ blood shows them to appear entirely compatible.

Discussion

It is of considerable interest that in this series of 6 mothers there were only 8 normal infants out of a total of 26 pregnancies. This observation fully confirms the finding of Levine, Katzin and Burnham² and it is safe to assume that the bulk of high fetal and neonatal mortality observed in the series of Rh- mothers can be attributed directly to the mechanism of iso-immunization.

In addition to the 7 definite cases of erythroblastosis fetalis, there were 6 more in which this diagnosis is probable. To cite a typical example, patient C. N. had had 2 nonmacerated stillbirths, three apparently normal term infants, and then 3 macerated infants. The last pregnancy resulted in a premature macerated infant. It is extremely significant that the blood of this mother was Rh-. The father's blood was not available for examination.

During the 16 months' period of this work, there were 2,000 deliveries of which 162 resulted in stillbirths or early neonatal deaths. In 61 of these deaths, the infant weighed less than 3 pounds. While blood was not secured from each mother who had a stillbirth or neonatal death, blood was obtained and studied for the Rh factor whenever the diagnosis of erythroblastosis fetalis seemed likely. Hence, 7 of 162, or 4.4 per cent of the stillbirths and early neonatal deaths, were definitely due to erythroblastosis fetalis, and in addition 6 cases, or 3.8 per cent, were probably due to this condition. One can thus conclude that the incidence of erythroblastosis fetalis in our series of 162 consecutive stillbirths and neonatal deaths is somewhere between 4.4 per cent and 8.2 per cent.

Although these values indicate that erythroblastosis fetalis is the underlying cause of a comparatively small proportion of random stillbirths, they at the same time support Levine's contention that the incidence of erythroblastosis fetalis will be considerably higher if based on the results of Rh tests.¹⁶ Javert¹⁷ stated that erythroblastosis fetalis as diagnosed on clinical and pathological criteria occurs once in 438 full-term pregnancies, but the results of this study based on Rh tests indicate an incidence of about 1 in 200 deliveries.

Intrauterine Death Occurring Well in Advance of Labor

There were 24 macerated fetuses in our series, and these included every case in which fetal death appeared at all likely to have been due to iso-immunization by the Rh factor. Of the 24 mothers, 7 or 29.1 per cent were Rh-. In 4 cases, or 16.6 per cent, the intrauterine death was definitely due to erythroblastosis fetalis, and in 3 cases, or 12.5 per cent,

this diagnosis was probable. Unquestionably, fetal death in utero is frequently due to hemolysis of Rh+ fetal blood by the maternal anti-Rh agglutinins. When maceration occurs, the cause of the fetal death usually cannot be determined at autopsy, and the diagnosis of erythroblastosis fetalis can only be suspected because of the serologic findings in the mother. In our relatively small series of 24 cases of fetal death in utero occurring well in advance of labor, the incidence of erythroblastosis fetalis is somewhere between 16.6 per cent and 29.1 per cent. A history of repeated macerated infants should arouse suspicion of erythroblastosis fetalis. In fact, it was because Levine noted that many mothers who harbor a dead fetus possess intragroup agglutinins and frequently experience blood transfusion reactions, that this study was begun and later led to the discovery of the true nature of iso-immunization of the mother by the fetus.

Toxemia of Pregnancy

A number of years ago several workers claimed that eclampsia was in some way related to a blood incompatibility of the fetus and mother.* In 1902 Flexner¹⁸ suggested that the agglutination of red blood corpuscles was the precipitating cause for the thrombosis which produced the periportal necrosis of eclampsia. In 1905 Dienst¹⁹ suggested that the fetal red blood cells can enter the maternal circulation, and be agglutinated. MeQuarrie²⁰ and Allen²¹ independently at the Johns Hopkins Hospital studied the question of iso-agglutination of the fetal and maternal blood and came to opposite conclusions. John Whitridge Williams²² did not believe that fetal blood entered the maternal circulation and appears to have discouraged further work along this line. Nevertheless, we now know that the fetal red blood cells can enter the maternal circulation, at least in minute quantities which nevertheless suffice for the iso-immunization.²³ That maternal antibodies enter the fetal circulation is a fact that has long been accepted.

With our present knowledge of iso-immunization it would seem plausible that fetal erythrocytes might be agglutinated in the maternal circulation by specific agglutinins produced by the immunized mother, and thereby cause liver and kidney damage with the ensuing symptoms of pre-eclampsia and eclampsia. With this theory in mind the blood of 2 eclamptic mothers was investigated. Both were Rh+. In addition, 5 cases of severe pre-eclampsia were studied, and in 4 the maternal blood was Rh+. Hence, the above theory is apparently disproved at least for some cases of specific toxemia of pregnancy. Yet, of the 7 definite cases of erythroblastosis fetalis in our series, in 5 the mother had mild to moderate pre-eclampsia. Of the 6 probable cases of erythroblastosis fetalis, in 4 there was mild to moderate pre-eclampsia. In this connection it is

*An excellent discussion of this subject was presented by Ottenberg. (J. A. M. A. 81: 295, 1923.)

of interest to recall the observation of Hellman and Hertig²⁴ and Javert¹⁷ that one-third of mothers of infants with fetal hydrops suffer from toxic symptoms.

We do not as yet feel that the theory of iso-immunization as the important factor in the etiology of eclampsia should be discarded without further investigation. Further studies are indicated taking into account also the possibility of iso-immunization by blood factors other than Rh.

Further Studies

From case histories one surmises that women who have infants with erythroblastosis fetalis also have a high incidence of spontaneous abortions (Maeklin²⁵), thereby suggesting a role for the Rh factor in the etiology of abortions. With this in mind, 9 mothers were examined who had had 2 or more early abortions in succession. Eight of these nine mothers were Rh+. By the mechanism of erythroblastosis fetalis the Rh factor not uncommonly causes death of the fetus in the second trimester and thereby produces a late abortion. These preliminary studies indicate, however, that the Rh factor is unimportant in the etiology of early abortions. This is rather surprising since the Rh factor can be shown to be present in the very early fetus.²⁶ A fuller discussion of this subject is given elsewhere.²⁷

Four women were studied who had had a tubal pregnancy, two of them having had 2 such gestations. All four patients were Rh+.

Two mothers in our series had a hydatidiform mole, one had several children afflicted with Cooley's anemia, and one had children suffering from hemolytic jaundice. One Negress had sickle cells in her blood (sickleemia). Six mothers had infants with various congenital anomalies, such as hydrocephalus, anencephalus, harelip and cleft palate, etc. In all of the above cases the Rh factor appears unimportant, for the bloods of all the mothers were Rh+. However, other workers have observed a higher than normal incidence of congenital malformations in erythroblastic infants.^{17, 28}

Eleven premature infants were studied. In 6 instances the mother had had repeated premature or immature infants which otherwise were apparently normal. In only one case was the mother Rh-, and this is listed as a probable case of erythroblastosis fetalis. The infant became clinically jaundiced on the day after birth and died, but post-mortem examination did not reveal any definite cause for death except prematurity. While infants with erythroblastosis fetalis are often premature at birth, most cases of prematurity in this study appear unrelated to the Rh factor.

In 4 cases of our series there was a premature separation of the normally implanted placenta. In all 4 cases, a stillbirth was delivered. In two the fetuses were badly macerated at birth. In these 2 instances the cause of death was erythroblastosis fetalis, as evidenced by the presence

of anti-Rh agglutinins in the maternal serum. The fetal death almost certainly antedated the premature placental separation. In the other 2 cases, the stillbirths were not associated with erythroblastosis fetalis and showed only aspiration of amniotic fluid as the cause of death. Although most cases of premature separation of the normally implanted placenta do not appear to be accompanied by erythroblastosis fetalis, analysis of a longer series is indicated.

As pointed out by Levine⁴ a statistical approach is now available to determine whether or not any of the pathologic conditions of pregnancy or the neonatal period are manifestations of iso-immunization of the mother by the fetus. This study is limited to the Rh factor as detected by human anti-Rh serum which gives 85 per cent positive reactions. Future studies should be based also on the finer differences of the Rh factor and should take into account the fact that other blood factors such as A, B, Hr, and possibly still others, may also induce iso-immunization of the mother with resulting damage to the fetus.²⁹

Conclusions

1. It is clearly established that in most instances erythroblastosis fetalis is produced as a result of iso-immunization of the Rh- mother by Rh+ fetal erythrocytes. The action of maternal anti-Rh agglutinins on the susceptible fetal red cells is the source of the hemolysis in the fetus during intrauterine life.

2. Correlating clinical and serologic findings, studies at Bellevue Hospital for a period of 16 months indicate that among 162 consecutive stillbirths and neonatal deaths, the incidence of erythroblastosis fetalis is somewhere between 4.4 per cent and 8.2 per cent.

3. Rh studies indicate that the incidence of erythroblastosis fetalis in this series is twice that hitherto given on the basis of clinical and pathological diagnosis.

4. In cases of intrauterine death occurring well in advance of labor, as evidenced by fetal maceration, the incidence of erythroblastosis is somewhere between 16.6 per cent and 29.1 per cent. This series of 24 cases includes only instances of unexplained intrauterine death of the fetus.

5. Studies of a relatively small series of cases indicate that the Rh factor is important in the production of late but not of early abortions, and that it is unimportant in the etiology of hemolytic jaundice, sicklelemlia, hydatidiform mole, and ectopic pregnancies. While infants with erythroblastosis fetalis are often premature at birth, most causes of prematurity appear unrelated to the Rh factor.

6. Proof for the possible relationship of blood incompatibility of the mother and her fetus to eclampsia and specific toxemia is still to be provided.

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SPINAL ANESTHESIA FOR CESAREAN SECTION

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THE present report is based on a study of 565 consecutive and unselected cases of cesarean section in 345 of which spinal anesthesia was used. The period covered was from 1935 through 1942, inclusive. There was no mortality in the series attributable to the anesthetic.

Despite this, it is not our intention to suggest that the indiscriminate employment of spinal anesthesia in this operation remains devoid of hazard. It is of paramount importance to recognize that there are contraindications to its use. It is not an agent for the inept or careless anesthetist. Yet the results on which this report is based would indicate that spinal anesthesia, because of specific proved advantages, has earned a place in cesarean section.

Method

One hundred mg. or less of procaine dissolved in 2.5 to 3 c.c. of spinal fluid produce sufficient duration of anesthesia to complete most cesarean operations. This dose should not be exceeded but frequently in smaller subjects or when a simple classical operation is contemplated, may be decreased to 90 or even 75 mg. with satisfactory results. In cases where additional procedures, such as tubal sterilization or myomectomy, are to be done, or in repeat sections in which adhesions may be expected to prolong operating time, the dose should not be less than 100 mg. It is important that the source of the drug be thoroughly reliable. In the interest of the infant, preoperative medication by morphine or the barbiturates is omitted. In the mother, too, these drugs may tend to depress the respiratory center and accentuate the hypotensive state. Infrequently when the operation is prolonged or for some less obvious reason the anesthetic wears off prematurely, and it becomes necessary to supplement it, nitrous oxide with or without ether is used. This occurred in 26 of our 345 cases, or 7.5 per cent. Even in this group the intraperitoneal work has usually by this time been completed so that only enough general anesthesia is required to effect closure of the wound. It is by all means safer to tolerate this possible inconvenience than to administer a larger dose of procaine with a view to prolonging the anesthesia. Supplementary use of general anesthesia may often be avoided by morphine sulfate, gr. $\frac{1}{4}$, hypodermatically given directly after extraction of the infant or later, by which time the spinal anesthetic has become fixed, and the danger of respiratory depression from it has passed.

The patient may be in the left lateral position, or sitting with the back arched. In the latter position the canal is more readily entered in some cases, though facility of puncture in the lateral position, which is preferred, is also readily acquired. Syncope of emotional or other origin attributable to the sitting posture has been rare. After slow in-

jection in the sitting position, it is a wise precaution to lower the patient slowly in order to avoid abrupt upward diffusion of the anesthetic. The injection should not be completed in less than 30 seconds. The fourth lumbar interspace is chosen in most cases; the third is used only when difficulty is encountered in the former. Of inestimable importance as a factor of safety is the rule not to inject above the third space. This minimizes the danger of depression of the respiratory center or the phrenic and intercostal nerves. Throughout the operation the table is maintained level because in former years a higher incidence of unfavorable reactions was noted with the Trendelenburg position.

To forestall a sharp drop in blood pressure and associated faintness, a preliminary injection of ephedrine sulfate (gr. $\frac{1}{2}$ to $\frac{3}{4}$) is given fifteen minutes before the spinal tap. An additional prophylactic measure is the intravenous infusion of 10 per cent glucose in saline or in distilled water which is begun immediately after the anesthetic has been injected and at least five minutes before the incision is made. Its analeptic action is less pronounced but more sustained than that of the ephedrine. A drop in blood pressure to 80 mm. Hg or less during the operative procedure is an indication to reinforce the original ephedrine injection. The repeat dose, however, is given intravenously to ensure prompt action, but in one-tenth the original dose. Exceptionally it is necessary to give a third injection in the same amount as the second. The repeat injections of ephedrine are readily given through the properly sterilized rubber tubing already in use for the intravenous glucose infusion. If the patient complains of a sense of constriction in the throat or experiences difficulty in breathing, or if the anesthetist observes by repeated routine skin testing a rising level of anesthesia well above the umbilicus, oxygen inhalation should be initiated at once and maintained until these subjective and objective phenomena have completely disappeared. They rarely endure more than a few minutes. Carbon-dioxide inhalation is not advocated because by its dilatation of the peripheral vascular tree, it is likely to accentuate the hypotension. Preoperative use of ephedrine is omitted in those patients whose blood pressure is 150 mm. Hg or higher. There has been no need to resort to artificial respiration in this series.

Advantages of Spinal Anesthesia

The following points of superiority of spinal over other forms of local or general anesthesia have been observed:

1. Ease and rapidity of administration, relative rapidity of effect, and more complete anesthesia. One needle puncture and a few minutes of waiting, during which the patient is draped, suffice. Local anesthesia is not as effective in relieving pain, particularly when the peritoneum is under tension, and commonly necessitates interruption of the operative procedure for the purpose of injecting additional anesthetic solution. That large amounts of novocain locally are not wholly devoid of danger is attested to by the not infrequent reactions and occasional fatality following its use. Though local anesthesia was used in 75 sections of this series, the preference for spinal remains.

2. The operating time with spinal anesthesia was less than with general or local. The average operating time of a classic section under spinal was 35 to 40 minutes; under general, 40 to 45 minutes; under local, 55 minutes. The same relative advantage in time for spinal anesthesia existed in the low two-flap operations which in general took 10 minutes longer to complete than the classic irrespective of the type of anesthetic used.

3. The "silent abdomen" in which intestinal calm pervades the field. No obtruding bowel appears over the uterus to impair technique or prolong operating time.

4. Better hemostasis due to a more firmly contracted uterus, a positive advantage in cases previously depleted by hemorrhage.

5. A conscious patient whose subjective reactions are readily elicited.

6. The testimony of patients who have had both spinal and local anesthesia that they suffered less with spinal. On repeat cesarean, the patient usually requests spinal anesthesia.

7. Early postoperative tolerance for fluids. Liquids parenterally do not vie with sips of water in assuaging the parched tongue. Furthermore, intravenous fluids postoperatively are less often required than with general anesthesia.

8. Less postoperative distension and little or no nausea and vomiting, which result in:

9. Less strain on the wound, better healing, and therefore:

10. A shortened period of hospitalization by an average of 2 days.

11. Greater adaptability of spinal anesthesia to patients suffering from various upper and lower respiratory tract afflictions contraindicating inhalation anesthesia: such as rhinitis, pharyngitis, tuberculous or neoplastic disease of the larynx, asthma, chronic bronchitis, chronic pleuritis, arrested lesions of the lung, and others. It is also more suitable than general anesthesia in those with organic disease of the heart, kidney, cardiovascular system, diabetes, thyrotoxicosis, toxemia of pregnancy, and to those exhibiting an undue dislike or dread of general or local anesthesia.

12. The absence from the uteroplacental circulation of any anesthetic protoplasmic poison is an advantage to the infant and mother, especially in toxemia.

Disadvantages

1. Four patients in this series expressed great dread of spinal anesthesia. In such instances spinal was not given.

2. Uncontrollability, due to too wide a diffusion of the procaine, is a valid objection. It can be minimized by adhering to the technique and dosage described.

3. In 30 per cent of the cases an episode of retching was observed about ten minutes after the injection. This is transient, rarely enduring

over a few minutes, during which it is best to interrupt the operative procedure. The field is covered with a warm, moist pad and the operator stands by. Forceful handling of the tissues during the retching spell prolongs its duration, inflicts trauma, and saves no time. If the anesthetist will urge the patient to take deep breaths of oxygen and to desist from retching or vomiting efforts, the incident passes off shortly.

4. The systolic pressure fell to 80 mm. Hg or less in 31 of the 345 cases, or 8.9 per cent. The average drop in the 31 cases was 50 mm. in systolic and 33 in diastolic pressure. In the remaining cases the fall in pressure averaged 30 mm. in systolic, and 18 in diastolic pressure. In both groups the response to treatment was satisfactory.

5. Difficulty in breathing was mild and transient when it occurred. Prophylaxis and treatment have already been given.

6. Limited duration of anesthesia was a practical objection in 26 cases. One hundred mg. of procaine produce anesthesia usually lasting 50 to 60 minutes which is enough to complete most operations. When supplementary general anesthesia is required it was observed that it takes longer to induce it than is the case with primary general anesthesia.

7. Postoperative headache occurred in 7 per cent of the cases. None persisted beyond the fifth postoperative day.

8. Complete failure of anesthesia was noted in 10 cases, or 2.9 per cent. Two cases of unilateral anesthesia occurred. Faulty injectional technique, defects in potency of the drug, or anatomic spinal anomalies may be responsible.

9. Mortality due to the anesthetic remains as a dangerous reality. No such instance, however, occurred in this series. The 4 patients who died were: (1) Patient with placenta previa who expired of complicating gastric hemorrhage on the twelfth postoperative day; (2) one with severe hypertensive toxemia who died on the ninth postoperative day; (3) death one day postoperative of uncontrollable post-partum convulsive toxemia; and (4) death on the second postoperative day of pulmonary embolism.

Cosgrove reported 244 abdominal sections done under spinal anesthesia with "no mortality in this group immediate or remote," attributable to the anesthetic. Brindeau in 1935 reported 100 cesarean sections performed under spinal anesthesia with no deaths or serious complications. He believes this form of anesthesia is ideal for cesarean section. A. Duca in pointing out the advantages of lumbar anesthesia in 86 cases of cesarean section stated that it has no danger or aftereffects. M. L. Perez and L. D. Guglielmo (Buenos Aires) used spinal anesthesia in 95 cesarean sections. The one death which occurred four hours after a cesarean section was due to toxemia and not to the spinal anesthesia. They state, "Not a single death could be attributed to the anesthesia." Add to these several series the 345 cases herein reported and the total is 870 cases of section done under spinal anesthesia without anesthetic mortality.

10. Neurologic complications or sequelae have not been observed.

Contraindications

1. Heart failure, coronary disease, and syphilitic aortitis.
2. Central nervous system disease.
3. Osseous disease or marked deformity of the spine.
4. Lumbosacral infection interfering with aseptic puncture.
5. Septicemia.
6. Psychosis or serious neurosis.
7. Hypotention persisting below 100 mm. Hg systolic after subcutaneous injection of $\frac{3}{4}$ gr. of ephedrine.
8. Hypertension above 180 mm. Hg systolic if associated with arteriosclerosis.
9. Shock.
10. Severe anemia.
11. Absence of an experienced anesthetist capable of promptly recognizing and dealing with unfavorable reactions; and
12. Absence of oxygen supply and apparatus for protracted artificial respiration.

Summary

The report is based on a study of 565 consecutive and unselected cases of cesarean section in 345 of which spinal anesthesia was used.

There was no mortality attributable to the spinal anesthetic.

Although 220 of the entire series were performed under other types of anesthesia, the preference has been for spinal.

The drugs used, their dosage, and the technique of injection are detailed.

The incidence and treatment of unfavorable reactions, and precautionary measures for their prevention are given.

The reasons for the preference of spinal anesthesia and its objections and contraindications are presented.

Acknowledgment is due Dr. Leo S. Schwartz, Chief of Staff, for his valuable help in the composition of this report. To the several staff members whose case records have been utilized, thanks are hereby tendered. For the task of collecting fundamental data credit is fully accorded to Miss Roselle Wolfson.

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AN EVALUATION OF THE TRANSVERSE CERVICAL CESAREAN SECTION

A Report Based on a Study of 208 Cases

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ALL low cervical cesarean sections may be grouped into two types, according to the low segment approach, namely, the first, trans- or intraperitoneal and second the extraperitoneal. Peritoneal exclusion operations are in reality of the intraperitoneal type. Again in each type, the lower uterine segment may be entered with a longitudinal or transverse incision. Among the various extraperitoneal operations, the Latzko operation employs the longitudinal incision and the Waters operation utilizes the transverse. Enthusiasm for the latter operation has increased interest in the transverse incision.

There are two questions which are unanswered to many of us: (1) Is the extraperitoneal approach safer for those cases having had tests of labor, the so-called potentially infected cases? (2) If a frankly infected case is terminated abdominally, what is the safest operation to use? Proponents of the extraperitoneal approach are probably too enthusiastic. For instance, in their recent book, Ricei and Marr make the statement, "the extraperitoneal approach eliminates the commonest type of fatality following cesarean—generalized peritonitis," and again, "this type of delivery, the extraperitoneal retrovesical approach, is no more than a vaginal delivery performed suprasymphysially." Obstetric literature does not corroborate either statement.

This author is in agreement with Gordon and Rosenthal who state, "there is reason to believe that the amniotic spill is not nearly as important as the remaining infected uterine as a cause of fatal sepsis."

This paper does not attempt in itself to answer the above questions but is simply the results of the author's experience with the intraperitoneal transverse cervical cesarean section. It comprises the facts concerning the 208 sections of this type performed by him since 1931. In every case the peritoneal cavity was exposed to amniotic fluid.

To Beck and DeLee go the credit for popularization of low cervical cesarean section in this country. The first reference to the transverse cervical cesarean section that I have seen in American literature was made by John Polak in 1926. In discussing a paper by Phaneuf, Polak stated as follows, "Mouro-Kerr has demonstrated recently what I believe is the last word in low section, namely, the transverse uterine incision through the thinned out cervical segment." The following year Phaneuf published his technique using the semilunar transverse incision and in 1931 he reported 198 cases with a maternal mortality of 3 per cent and a fetal mortality of 4.5 per cent. In 1935 Hefner

reported 150 cases with no maternal mortality while in 1936 Phaneuf published a paper with an additional 160 cases with one maternal death. In an analysis of all cesarean sections done at the Coleman Hospital from 1927 to January 1, 1936, by several operators, this author reported in 1937, 88 transverse cervical cesarean sections with a maternal mortality of 3.4 per cent. Among other reports on transverse operations were those by Acosta-Sison in 1937 and of Leighton in 1938. Among those favoring the operation today are Stander, Waters, Gordon, and Phaneuf. However, many of the large obstetric services have preferred the longitudinal low cervical operation and, despite the large number of papers on cesarean section, there have been comparatively few concerning the transverse cervical type.

The present series then represents all of the transverse cervical cesarean sections personally performed by the author. These operations were done at the four Indianapolis hospitals and were distributed as follows: St. Vincent's Hospital, 27; Indianapolis City Hospital, 9; Methodist Hospital, 101; and Coleman Hospital, 75.

Technique

Preoperative Preparation.—In the elective cases, each patient was especially prepared the evening previous to operation. In addition to a soapsuds enema, perineal and abdominal shaving, the abdomen was prepared by scrubbing with green soap and ether. Then tincture of merthiolate was applied and the abdomen covered with sterile towels. A barbiturate, such as amytal, was given that night for sleep. The next morning a catheter was anchored and left open to drain during the operation. Sodium amytal, gr. vi, and atropine sulphate, gr. $\frac{1}{150}$, were given three-quarters of an hour before the schedule time for operation. No vaginal antiseptic was used in any of the cases. Just before operation the abdomen was again scrubbed with green soap, ether and tincture of merthiolate applied.

If patients had had a test of labor, often an intravenous injection of dextrose in sterile water was given preoperatively. The abdomen was also prepared as in the elective case but time interval between preparation was shorter.

Operative Technique.—Our technique has been essentially the one that Phaneuf described, differing slightly in three points. First the visceral peritoneum and bladder have been dissected downward fully as far as if one were doing the longitudinal incision. Occasionally, after a previous longitudinal low cervical section, this is impossible as the visceral peritoneum will be so adherent to the lower uterine segment. We have felt that our patient was safer if we could start the incision just as low on the lower uterine segment as possible and then bring it curving upward on either side. The second point is that in the last 116 cases I have routinely thoroughly examined the interior of the uterus for evidence of abnormal placental implantation, evidence of submucous fibroid, or unsuspected injury to the uterus. The necessity for this was pointed out by this author last year but deserves re-emphasis. Since this has been done there has been no increase in morbidity and the procedure is an increased safeguard to the patient. The third point is that sponges were not used to wall off the uterus

as I believe that the spill is of little or no importance in the production of infection. The ability of the peritoneum to withstand one initial insult is too little appreciated.

The uterus was not packed routinely but only on indication such as in cases of placenta previa or abruptio placentae. In my experience, routine packing of the uterus leads to increased morbidity.

Postoperative Care.—Intravenous dextrose, usually a 5 per cent solution in sterile distilled water, was given every eight hours until the patient had been able to take adequate amounts of fluid by mouth. The first 24 hours, only tap water was permitted, the second day, hot unsweetened tea and fat-free broth if the patient was hungry. Usually the indwelling catheter was kept in place until 6 hours before the first enema which was given on the third postoperative day. After the initial enema, soft diet was permitted. By delay in feeding, it has been our experience that the patient is more comfortable and has fewer gas pains. Enough morphine is given to keep the patient comfortable. In only two of the cases was distention so great that the Wangenstein suction apparatus was used. If the patient runs an afrebrile course, we do not disturb the abdominal dressing until about the tenth day when skin clips or black silk are removed. Usually a high back rest is given on the tenth day, a slight elevation permitted shortly after operation and the patient sits in the chair on the twelfth or fourteenth day.

Disadvantages of the Transverse Incision

In cases where large varicosities are present on the lower uterine segment, we have favored the longitudinal incision because obviously a smaller amount of bleeding will be encountered if the incision can be placed between varicosities instead of across them. Bleeding is also apt to be much greater if the transverse incision is used in placenta previa when the placenta is located on the anterior wall. However, with the abdomen opened, particularly in cephalic presentation, one can usually tell whether placental tissue intervenes between the anterior wall and the baby's head, before the incision is made. If in making the incision large sinuses are encountered, bleeding may easily be controlled by application of Kelly clamps.

Much has been written about the possibility of extension of the incision through the large uterine vessels. We have never encountered this, though in one or two cases we have been surprised to find a small opening in the broad ligament without extension of the uterine incision. These were sutured and no harm was done. In three cases where there was extension of the incision, the extension was downward in the midline of the lower uterine segment. In each case the extension was simply repaired with interrupted sutures.

Thrombophlebitis occurs after this type of incision as it does in all cesarean sections. However, the only fatal case of pulmonary embolism that I have had after cesarean section was after a longitudinal low cervical section.

We have rarely had difficulty in approximating the uterine edges

because of difference in thickness. Especially is this true when the incision is started as low in the lower uterine segment as possible.

Advantages of the Transverse Cervical Cesarean

Easier Extraction of the Baby.—It is a simple geometric fact that the transverse incision made in the lower uterine segment is much larger than a longitudinal incision in that same lower uterine segment can possibly be. While it is true that in many cases the lower uterine segment is long enough for an adequate longitudinal incision, there are many cases, particularly of the elective type, where such is not the case. Usually it is not necessary to apply forceps in the transverse cervical while in the longitudinal, the opposite is true. There is a certain small percentage of cesarean section babies that die from intracranial hemorrhage or become cerebral spastics. While in many cases the forces of labor during a trial labor may have damaged the baby, still it seems logical to use an adequate incision.

Protection Against Infection.—If a longitudinal incision has to be extended toward the fundus or is inadvertently torn in that direction so that the visceral peritoneum cannot cover the entire incision, obviously the advantages of the low cervical operation are nullified. That accident does not happen after the transverse incision and I have never seen a transverse incision that was not kept entirely in the lower uterine segment. Neither have I witnessed peritonitis in a patient having had the transverse incision. Neither series of Phaneuf showed peritonitis in the transverse cervical cesareans, but 1 of 2 of his extraperitoneals reported, died of peritonitis. It is my firm opinion that we do not have to fear entering the peritoneal cavity if the wound we leave in the uterus is so placed that, should suppuration occur in it, there will be no communication with the peritoneal cavity. A patient with an infected uterine wound placed retroperitoneally with inadequate drainage may die from sepsis but rarely from peritonitis.

Indications for Operation

My attitude toward indications for cesarean section has been given in a previous paper.⁵ Table I gives indications for the operations in this series.

Parity of the patients in this series is given in Table II. Of those patients who had had previous cesarean, 19 had 1 previous classic operation, 23 had 1 previous transverse cervical operation, 2 had 1 previous longitudinal low cervical, 2 had 2 previous classics, 3 had 2 previous transverse cervical operations while 1 had had 1 previous classic and 1 previous longitudinal low cervical operation.

Anesthesia

No patient lost her life because of anesthesia though one patient having had cyclopropane went into profound shock some two hours after the operation. Types of anesthesia used in this series are shown in Table III.

TABLE I. INDICATIONS (TOTAL 208)

1. Previous cesarean section	50
2. Contracted pelvis with disproportion (1 brow presentation)	84
3. Diabetes	8
4. Breech, para i, large baby, borderline pelvis	18
5. Pre-eclampsia	23
6. Eclampsia	2
7. Chronic vascular renal disease	1
8. Chronic glomerular nephritis with toxemia	1
9. Placenta previa	7
10. Abruptio placentae	4
11. Organic heart disease	3
12. Previous amputation of cervix	2
13. Transverse presentation with uterus arcuatus	1
14. Unexplained intrauterine death of first baby near term	2
15. Prolapse of cord	2

TABLE II. PARITY OF PATIENTS

Para i	133
Para ii	63
Para iii	10
Para iv	1
Para vi	1

TABLE III. ANESTHESIA

Cyclopropane	68
Ethylene	33
Ether	44
Local	16
Nitrous oxide ether	47

Transfusions

One hundred and seventy-four did not require transfusions while 25 patients had 1 transfusion, 8 had 2 transfusions, and 1 patient required 3 transfusions. It is very much worth while to have the patient typed and a donor ready, especially if that particular hospital in use does not have a blood bank.

Maternal Mortality

There were two mothers lost in this series, giving a mortality of less than 1 per cent, namely, 0.96. One patient was lost from postoperative hemorrhage due to my lack of appreciation of the extent of the pathology. The patient had a placenta previa cervicalis inereta and this was her second section. Hysterectomy should have been done.

The other case was one of organic heart disease of long standing. The cardiologist and I decided to permit labor and after 12 hours decompensation occurred. Compensation could not be restored and section was done in the interest of the baby, the mother dying 12 hours later.

It is significant that no mother died of infection of peritonitis.

Fetal Mortality

Two hundred and ten children were delivered and 7 did not survive. Two babies were stillborn and 5 were neonatal deaths. The fetal mortality was 3.3 per cent. Causes of death are shown in Table IV.

TABLE IV. FETAL DEATHS

Prolapsed cord	1
Hydrocephalus (x-ray was not convincing)	1
Abruptio placentae	1
Diabetes of mother	1
Atelectasis and congenital heart	1
Prematurity	1
Spina bifida	1

Maternal Morbidity

The Elective Case.—There were 105 cases in the series of this type, 77 cases showing no morbidity and 28 that had morbidity, an incidence of 26.6 per cent. The standard used was that of the American Committee on Maternal Welfare. While many would question the advisability of doing anything but a classic section in this group, I prefer the low cervical because of the smooth convalescence, the lowered incidence of adhesions, and the increased safety of the scar in following pregnancies.

Cases Having Had Tests of Labor.—Table VI shows morbidity of all cases according to hours of labor, Table VII giving morbidity according to cervical dilatation and Table VIII according to condition of membranes. Even with x-ray pelvimetry, we consider tests of labor in borderline cases as essential to the lowest incidence of cesarean section.

The Infected Patient.—This author still believes that the Porro operation is the safest procedure in the frankly infected patient. As long as the uterus remains with an infected incision in it, whether the operation has been extraperitoneal or intraperitoneal low cervical, there is definite danger of sepsis. Fortunately, this type of case is now rarely seen.

TABLE V. MORBIDITY IN CASES HAVING ADDITIONAL OPERATIVE PROCEDURE

	MORBIDITY	NO MORBIDITY	TOTAL
Cornual resection	3	14	17
Madlener sterilization	2	5	7
Irving sterilization	2	2	4
Bilateral salpingectomy	1	4*	5
Myomectomy		2	2

*One previous Madlener; 1 previous cornual resection.

TABLE VI. MORBIDITY ACCORDING TO HOURS OF LABOR

	MORBIDITY	NO MORBIDITY
Elective	28	77
1 to 6 hours	6	5
7 to 12 hours	10	15
13 to 24 hours	16	22
25 to 48 hours	14	14
48+ hours	1	

TABLE VII. MORBIDITY ACCORDING TO DILATATION OF CERVIX

	MORBIDITY	NO MORBIDITY
0 to 2 cm.	28	77
3 to 5 cm.	19	20
6 to 9 cm.	20	33
Complete	8	3

TABLE VIII. MORBIDITY ACCORDING TO CONDITION OF MEMBRANES

	MORBIDITY	NO MORBIDITY
Intact	53	109
Ruptured for		
1 to 6 hours	6	5
7 to 12 hours	6	4
13 to 24 hours	6	9
25 to 48 hours	4	6

TABLE IX. KNOWN CAUSE OF MORBIDITY

Wound infection	10
Cystitis	3
Thrombophlebitis and pleurisy with effusion	1
Thrombophlebitis	3
Lochiometra	2
Endometritis	6
Pyelitis	12
Upper respiratory infection	2
Gastroenteritis	1
Massive collapse of lung	1

The greatest risk that I have subjected a patient to is in this series. Forceps had been applied in the home by her physician and I also attempted forceps in the hospital. Station was about -1 and the pelvis very flat. In spite of proper application, the head would not enter the pelvis. The uterus was tetanically contracted so as to contraindicate version. The baby was in good condition. A transverse cervical section was done and a live baby obtained. The patient made a nice recovery except for a slight abdominal wound infection. Incidentally, she has never again become pregnant so that conservation of the uterus in these cases is, in some instances, theoretical conservation only.

Another case had had a previous transverse cervical cesarean after forceps had been applied and failed, by another operator. She did not develop peritonitis and at the time I operated upon her had no adhesions.

A third case in this series was operated on after many hours of labor and with membranes ruptured several hours. The fetus and interior of the uterus both had a foul odor and infection was obviously present; yet no peritonitis developed.

The resistance in intraperitoneal low cervical operations against peritonitis is also illustrated by case 10643 (M.H.). Her second cesarean, a transverse cervical, is in this series. With her first pregnancy at term she developed an acute appendicitis. A suppurating appendix (not ruptured) was removed. Two days later labor started and was very painful. She had a dystocia dystrophia syndrome-type pelvis, and after 24 hours the head had made no attempt to enter the pelvis. A longitudinal low cervical cesarean was done. The patient developed a wound infection but made a good recovery without developing any evidence of peritonitis.

Vaginal Deliveries Following Cesarean Section.—In this series, 4 patients have since delivered vaginally. A para ii operated upon for placenta previa has since had 2 normal deliveries. Another para ii operated upon for the same reason has had a normal delivery. Two primiparas operated upon respectively for fulminating pre-eclampsia and prolapsed cord have since delivered vaginally. We have no knowledge of any rupture following any of the sections reported.

However, in the three women upon whom I have performed three transverse cervical cesareans, the entire lower uterine segment appeared very thin but no scar could be identified. Many of the cases having had previous classic operations showed wide, thin, easily identified scars. Also, adhesions were much more common in the cases having had previous classic operations.

Upon one patient I later performed a total hysterectomy. Sections were made down the lower uterine segment and the pathologist reported as follows, "Sections through the uterine wall at site of former cesarean closure show an architecture that is difficult to identify between that and ordinary uterine wall. Line of scar is broken and interrupted and blends into general architecture of the uterine musculature."

Summary and Conclusions

This study is based on 208 transverse cervical cesarean sections performed by the author since 1931. They were performed under average conditions in four Indianapolis hospitals, two of which have separate operating rooms for cesarean sections in the maternity department.

There were two maternal deaths in the 208 operations, a maternal mortality of 0.96. Neither death was due to infection nor peritonitis. One hundred and five of the cases were elective while 103 had been in labor from 1 to 48 hours. The cause of one death was hemorrhage and the other was due to cardiac failure.

Two hundred and ten children were delivered and 7 did not survive. Two babies were stillborn and 5 were neonatal deaths.

Twenty-three patients had 1 previous transverse cervical cesarean while 3 patients had had 2 previous transverse cervical cesareans. No ruptured scars were encountered.

Substitution of the extraperitoneal operation for the transverse cervical operation would not have lowered the maternal mortality in this series.

Adequate tests of labor may be safely given if the transverse cervical operation is used.

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ANDROGEN THERAPY IN PELVIC MALIGNANCY*

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THE management of patients having skeletal metastases from mammary cancer has always been difficult, but new hope for these patients was given by Ahlbom¹ in 1930, who advocated x-ray castration in this condition. Inasmuch as the effect of such treatment is to greatly diminish the amount of circulating estrogen and thereby leave a proportionately large amount of androgen in the blood stream, Lacassagne,² Raynaud,³ Murlin,⁴ and Nathanson and Andervont⁵ all suggested and published papers about their experiences in treating this condition with injections of the male hormone. Results were somewhat encouraging in that the individuals often appeared to be subjectively improved although the basic condition was not affected. Loeser⁶ recently presented his experiences in treating six similar patients by means of implantations of testosterone propionate or progesterone (both said to be antagonistic to the follicular hormone). Of the six cases, three had extensive metastases prior to therapy and two of these were seemingly partially arrested. The other three patients had no metastases, and none developed in the subsequent five years. In all these investigations, however, the results are by no means uniform and this type of therapy must still be considered to be in its experimental stages.

Since it is a well-known fact that the male sex hormone has a pronounced atrophy-inducing effect on the ovary, we submitted a small group of patients with ovarian carcinoma (also two other individuals with carcinoma of the cervix) to androgen therapy. These cases were hopeless from a clinical point of view and we felt that no harm could result from endocrine therapy. Unfortunately our observations had to be entirely clinical as we were unable to study these patients with hormone assays.

Case Reports

CASE 1.—C. R., 47, white, parous woman admitted to Temple University Hospital on August 4, 1942. She was found to have an early carcinoma of the breast as well as carcinoma of the ovary. X-ray studies demonstrated a probable beginning metastatic lesion in the spine and definite lesions in the lungs. A simple mastectomy and an exploratory laparotomy were performed. At operation a large, fixed, solid tumor, 23 by 33 cm., was found to be filling the pelvis and reaching to the umbilicus. The capsule was broken through and the surrounding tissue was already invaded. Biopsy revealed adenocarcinoma of the ovary. On September 4, 1942, testosterone propionate therapy was instituted (10 mg. three times per week). At this time her weight was 113 pounds. At the end of one week of such therapy the patient felt better, her

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†Neo-Hombreol was furnished by Roche-Organon, Inc.

strength was improved, and she had gained two pounds in weight. The dosage was increased to 20 mg. and finally 30 mg. three times per week until she had received a total of 270 mg. The patient continued to feel stronger and more comfortable although after one month of therapy she again began to lose weight. Six weeks after androgenic therapy was started she appeared to be better than at any time since she had been under our care. Suddenly, however, the patient developed extreme weakness and was unable to come to the clinic. She remained in bed at home and five weeks after the last injection of testosterone, a large amount of suppurative material spontaneously drained through the rectum and the abdominal mass disappeared, leaving only a "frozen pelvis" and no palpable mass. Meanwhile the patient had had no pain. Two weeks later she died probably of the pulmonary metastases. An autopsy was not obtained.

CASE 2.—H. F., 74, white, nulliparous patient was admitted to Temple University Hospital on March 4, 1942. Examination revealed a firm, fixed tumor mass in the pelvis, extending to 9 cm. above the symphysis pubis. Exploratory laparotomy revealed an inoperable carcinoma of the right ovary, with biopsy demonstrating adenocarcinoma of the ovary. She was given deep x-ray therapy over 2 portals, but the tumor did not regress. The patient was extremely feeble, weighing but 118 pounds. Although her weight remained constant there was no appreciable change in the patient over a period of six months. On September 17, 1942, testosterone therapy was started. Ten mg., then 20 mg., and finally 30 mg. three times per week were given. The mass at the beginning of treatment measured 22 by 28 cm. and the patient's weight was 118½ pounds. After three weeks of this therapy she was much stronger, her appetite was good, and in her own words she was "feeling fine." After five months of this treatment she had gained seven pounds but the growth had increased to 23 by 35 cm. A punch biopsy revealed the same cytology as before treatment. Therapy was discontinued after 1,310 mg. testosterone propionate had been given. At the end of one month without treatment the patient began to fail rapidly and was readmitted to the hospital, dying in cachexia May 27, 1943. Autopsy demonstrated a gross increase in the size of the carcinoma, and histologic sections showed the same structure as before therapy.

CASE 3.—F. F., 43, Negress, parous individual was admitted to Temple University Hospital December 20, 1942. A diagnosis of Stage IV carcinoma of the cervix was made. There were metastatic lesions in the bladder and throughout the pelvis. It was believed that nothing could be done for this patient except administering sedatives for pain. One to 1½ grains of morphine were required daily. On January 18, 1943, testosterone propionate (25 mg. daily) was started. Within forty-eight hours the patient no longer required morphine. Two weeks later increased nitrogen retention was noted and the patient died in uremia one month after testosterone therapy was instituted. A total of 700 mg. was given and at autopsy there was no change in the cellular structure from that seen on the biopsy taken at admission.

CASE 4.—W. D., 32, white nulliparous patient was admitted to Temple University Hospital on January 21, 1943. The patient gave a history of having had "some x-ray treatments" during the past six months for a mass in the lower abdomen. This procedure had been carried out without a diagnosis and the roentgen ray dosage was questionable. A

small exploratory abdominal incision was made on January 23, 1943, which revealed an inoperable solid carcinoma of the ovary. Biopsy proved the neoplasm to be adenocarcinoma. On January 25, 1943, testosterone therapy was initiated (25 mg. daily). The large abdominal mass did not regress although the patient was subjectively better. After 595 mg. of testosterone propionate had been given she was discharged from the hospital. At that time there was no evidence of secondary sex changes, and the patient continued the androgen therapy at home, receiving an additional 400 mg. She was readmitted to the hospital on March 15, 1943, and stated that she was stronger and in better spirits than ever. However, there was marked hirsutism, complete breast atrophy, and her voice was definitely masculine. There appeared to be no regression of the tumor and in spite of the apparent improvement in the patient we did not feel justified in continuing the testosterone. Deep x-ray therapy was started, 650 to 1250 R. over 4 portals being given. With this treatment the patient improved rapidly for a short time. However, ascites soon developed, the patient lost weight, developed anorexia, and when last seen on August 1, 1943, her condition was very poor.

CASE 5.—M. B., 50, white, nulliparous patient was admitted to Temple University Hospital on October 9, 1942. She was found to have a squamous cell carcinoma of the cervix (Grade III). Preliminary roentgen ray therapy (2,000 R. over 6 portals) was started. On December 9, 1942, she received a total of 6,600 mg. of radium applied to the cervix, fundus, and parametria. Her condition apparently improved until May 27, 1943, when she was found to have pulmonary metastases, with considerable chest and supra clavicular pain. Testosterone propionate 25 mg. three times a week was started, and before her death July 31, 1943, the patient had received a total of 275 mg. After her second injection the patient claimed to have felt better and her pain disappeared. No sedation was required at any time after testosterone was started.

CASE 6.—M. A., 53, white, parous patient was admitted to Temple University Hospital on December 11, 1942. She was operated on December 15, 1942, and was found to have an ovarian tumor with a large amount of serosanguineous fluid in the peritoneal cavity. The pelvis contained a large friable tumor of the right ovary. The uterus had multiple fibroids. The bladder, peritoneum, and cul-de-sac, as well as the bowel walls, were covered with metastatic implants. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. Histologic sections revealed a papillary adenocarcinoma of the ovary and uterine fibroids, and adenomyosis. The patient's condition was fairly good until about June 1, 1943, when she was readmitted. There was a large amount of fluid present with multiple nodules, noted by palpation, in the abdomen and cul-de-sac. Deep x-ray therapy over 2 portals (2,100 R.) was given, to no avail. On June 30, 1943, because of severe abdominal pain, testosterone propionate was started in doses of 25 mg. every day. After five injections she experienced severe nausea and vomiting, and the pain was unrelieved. Medication was discontinued but reinstituted two weeks later. The same reaction occurred after 125 mg. had been given and again therapy was stopped. This patient received a total of 250 mg. with very distressing effect. At present her condition is very poor.

Comment

Although the final results in these cases were identical to similar cases which did not receive androgenic therapy, I am of the opinion that this comparatively new method of treatment is definitely worth while. The pain experienced by these patients was almost completely relieved in the majority of cases and constitutionally, they were much improved as evidenced by their gain in weight. Such results cannot be expected from opiates and deep roentgen ray therapy. It is interesting to note that none of the cases demonstrated evidence of reduction in size of the neoplasm, nor were histologic changes found.

It is unknown how the male sex hormone brings about this improvement. However, it is known that there would appear to be a balance which normally exists between the amounts of male and female sex hormone in the body. If it is assumed that one of the factors in the production of cancer of this type is an excess of estrogenic substances in the body, it seems not unreasonable to expect that the administration of massive doses of androgens will counterbalance the excess of estrogens, perhaps causing the level of the latter to become even lower than normal. This should logically tend to inhibit the rapid extension of the growth. However, it did not. It is difficult to see how pain was so promptly and effectively relieved. Accordingly, until more evidence is accumulated, the treatment must be considered empirical. However, this should not be misinterpreted as implying that the therapy is not of value. We believe that it is, and would be interested in an extension of its use.

Summary

1. Six cases of pelvic malignancy have been submitted to testosterone propionate therapy.
2. Pain was rapidly and almost completely relieved in most cases, and the patient's general condition was improved.
3. Androgenic therapy should be further tried in cases of this type.

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ABSORPTION OF RADIOACTIVE SODIUM INSTILLED INTO THE VAGINA

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THE vaginal wall, with its thick stratified epithelium overlying the muscular and connective tissue layers, might appear to present a fairly formidable barrier to the absorption of drugs. This notion coupled with the fact that the lining of the vagina is relatively insensitive to pain has led to the widespread and often indiscriminate employment of many kinds of medicaments in the form of douches, tampons, and suppositories. Such self-administration of potentially potent pharmaceuticals, often as an act of desperation, is readily understandable. Physicians have often been guilty of condoning the practice, if not actually prescribing this form of medication, believing that the agents employed produce only a local effect. To be sure, many preparations used for douching are quite innocuous and acceptable to both the physician and the patient. However, it must be stressed that many preparations may be given with impunity only when used in proper dilutions and when the vaginal wall is relatively intact, and the cervical canal closed.

Women whose uteri have been removed continue to have moist vaginas. There may be no visible escape of moisture to the outside. This suggests both secretion and absorption of fluid by the vaginal wall. However, some evaporation at the outlet doubtless occurs. The familiar observation that the secretion of an hematocolpos released at the incision of an imperforate hymen of the postpubescent girl is thick, tarry, and much more viscid than normal menstrual blood, provides further evidence of fluid absorption by the vagina.

Robinson⁶ quotes an opinion that a substance or substances absorbed by the vagina from semen has been credited with constitutional improvement of certain patients. He also cites evidence that semen is retained postcoitally in mares and cows. And on this same subject, Duncan² writes as follows: "In the great majority of women, the semen is retained." Clear distinction between vaginal, cervical and uterine absorption is, however, not made. That the vaginal walls of certain rodents may be actually invaded by living spermatozoa has been demonstrated by Kohlbrugge.⁴ Robinson has presented experimental evidence that potassium iodide and sodium salicylate may be recovered in the urine within one hour following introduction into the vagina. Less rapidly excreted in the urine are quinine, cane sugar, and phenol red. Methylene blue, if absorbed at all by the vagina, is absorbed only in minute quantities. Macht⁵ has compiled an extensive list of published accounts which emphasize the toxicologic consequences of the absorption of various poisons through the vagina. In addition, he employed physiologic and chemical tests demonstrating that numerous drugs, poisons, alkaloids, inorganic salts, esters, and antiseptics may be absorbed from the

vaginal walls of the dog and eat. Cases of mercurial and phenol poisoning resulting from the use of strong vaginal douches are cited by Graves³ as evidence of the absorbing property of the vagina. By means of an immunologic method, Rosenzweig and Walzer⁷ were enabled to detect the almost immediate absorption of peanut protein from the human vagina and cervix.

In planning the present study the authors chose as a test substance a solution containing radioactive sodium. It was believed that such a preparation more nearly approximates a physiologic solution than many of the test substances which have heretofore been employed. It must be emphasized that concentrated solutions of foreign substances might well produce local changes, i.e., erosion or even ulceration. Absorption from such pathologic sites should not properly be construed as normal absorption. Another advantage of using the tagged sodium is that at subsequent recovery identification of the atom can be made with certainty.

Method

Radioactive sodium,* as sodium chloride, was introduced into the vaginas of seven women. The amount of salt instilled ranged from 105 mg. to 150 mg.; and about 10 c.c. of solution was used in each instance. To prevent leakage, the subjects' hips were slightly elevated, and a small cotton tampon inserted just within the vaginal outlet. Blood samples were then taken at frequent intervals from the cubital veins. Hematocrit readings of the oxalated blood were determined in each case for the estimation of plasma in the circulation. In the calculations, it was estimated that 72 c.c. of blood per kilogram of body weight is present in the circulation. Following centrifugalization, determinations of the radioactivity were made on the plasma, using a dipping type tube in conjunction with a Geiger-Miller counter.¹ A portion of the original sample, was, in each case, reserved as a pilot sample to determine the purity of the isotope and to refer the individual activity measurement to a convenient empirical zero time.

Results

The results of these experiments are illustrated in Table I. Wide fluctuations are noted in the amounts of sodium absorbed, and quantitative absorption cannot be demonstrated under the existing conditions. No parallelism is noted between the amount instilled and that recovered from the blood. No effort was made to determine the surface areas of contact of the test solution with the various vaginas. Furthermore, it would have been difficult to determine accurately the extent to which the vaginal and cervical mucosae were intact in any particular subject. The data, do, however, show the general range of absorption under certain conditions. Significant, we feel, is the observation that the greatest percentage of absorption occurred in the cases of women who had recently been delivered or whose vaginas and cervixes had been variously traumatized. It is at least strongly suggested by these experiments that the clinical condition of the vaginal wall and/or cervix may be the important determining factor which controls the amount of absorption. A normal, healthy vagina might well tolerate without detriment an antiseptic

*The authors make grateful acknowledgment to Dr. G. Dessauer of the Physics Department of the University of Rochester for the preparation of the radioactive sodium used in this study.

TABLE I. SHOWING THE PER CENT OF RADIOACTIVE SODIUM INSTILLED INTO THE VAGINA RECOVERED IN THE CIRCULATING PLASMA

SUB- JECT	TYPE OF CASE	AMOUNT OF RADIOACTIVE SODIUM INSTILLED MG.	INTERVAL BETWEEN INSTILLATION AND BLOOD SAMPLING								
			HOURS								
			1/2	1	1 1/2	2	3	5	18	22	24
A	Normal	105	.02	.04		.05					
B	Normal	105	.05	.09		.10					
C	Threatened abortion	110	.13	.46	.47				1.37		
D	Postoperative 12th day after subtotal hysterectomy	105	.05	.18	.24				1.5		
E	Postoperative 15th day after subtotal hysterectomy	150	3.5		1.0		1.1	1.2		1.2	
F	Post partum 9th day	150	.81		2.0		2.6	3.3			2.9
G	Post partum 10th day	105	.23	.41	.88				1.73		
H	Post partum 12th day	110	4.7	7.3	9.0				11.5		

douche which could cause serious disturbance when administered to a woman whose vagina or cervix remains bruised, lacerated, or otherwise traumatized as from a recent delivery, operation, or injury.

Summary

1. The use of radioactive sodium provides a delicate method whereby the transportation of this substance throughout the body may be accurately followed.

2. Radioactive sodium readily passes into the general circulation following its instillation into a traumatized vagina. Absorption from the intact vagina and/or cervix is less marked.

3. These experiments suggest the need for special caution in administering douches containing poisonous ingredients, particularly when the vagina and/or cervix have been recently traumatized.

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CONJUGATED ESTROGENS IN HUMAN PREGNANCY SERUM*

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IT IS well known that the estrogens in the urine of pregnant women are present almost entirely in the conjugated state. It has been estimated¹ that in the latter months of pregnancy up to 98 per cent of the urinary estrogens are in a conjugated form from which they may be freed by acid hydrolysis. In the bile of pregnant women the estrogens appear to be present almost entirely as free hormone.² That free estrogens are present in high concentration in the serum during the last trimester of gestation is also well known; there are few data available, however, to indicate whether the estrogenic potency of human pregnancy blood or serum can be increased by acid hydrolysis or other methods for demonstrating conjugated estrogens. The few data which are available are conflicting. The chemical nature of the estrogens in human pregnancy blood is not known and there is even a paucity of information concerning its distribution in the various components of the blood.

Albrieux^{3, 4} showed that the estrogens in human pregnancy blood are equally distributed between plasma and cells, although in nonpregnant patients the cells contain twice as much estrogenic hormones as plasma per unit volume. Numerous observations which we have accumulated in our laboratory also indicate that the concentration of free estrogens in serum and whole blood of pregnancy are identical.

Mühlbock⁵ first demonstrated that a portion of the estrogen in the blood of the pregnant mare is in a combined form. Later this investigator⁶ reported similar findings for human pregnancy blood. He examined two specimens of placental blood obtained at the time of delivery, two specimens from patients with late toxemia of pregnancy, and one specimen from a post-partum eclamptic patient. The blood was collected in a bottle containing alcohol, the latter was evaporated, and the residue extracted directly by warming with benzene, first in a neutral state to remove the free estrogens and then after hydrolyzing twice for 6 hours with 4 per cent HCl to liberate the conjugated hormone.

In a preliminary report⁷ we presented data demonstrating the presence of conjugated estrogens in serum of pregnant women. Our studies suggested that the estrogens in pregnancy serum were present in the protein fraction and were in part rather firmly "bound" to the protein.

On the other hand, Goldberger and Frank⁸ have recently reported that their attempts to increase the estrogen yield of pregnancy blood by

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hydrolysis were unsuccessful. These workers used citrated blood which was laked with distilled water and hydrolyzed at pH 2.0 by boiling for 15 minutes.

Material and Methods

Blood for these studies was collected from normal, healthy pregnant women during the last two months of gestation. The blood was allowed to clot and the serum was separated. In each case a portion of serum was assayed directly for free estrogen. The remainder was subjected to various procedures of extraction and hydrolysis. The following techniques were found to yield the best results:

The serum was acidified to pH 1.0 with concentrated hydrochloric acid and was heated in a boiling water bath for six hours. The gelatinous mass was then extracted three times by shaking for one-half hour with four volumes of an equal mixture of ether and alcohol. The ether-alcohol fractions were pooled, evaporated to dryness, and taken up in corn oil to a fixed volume for biologic assay. The remaining precipitate was dried and powdered; a portion of it was suspended in water and assayed similarly to determine the free hormone content of the residue. The remainder of the residue was subjected to further hydrolysis. Water was added, the pH adjusted to 1.0 and the suspension heated for six hours in the water bath, after which it was extracted with ether and alcohol and finally taken up in corn oil for biologic assay. In two of the experiments, the hydrolysis was carried out at pH 0.5; otherwise the technique was the same as above.

Preliminary experiments showed that ether-alcohol extracts of the serum without hydrolysis had the same estrogen content as whole serum, as has also been noted by Goldberger and Frank.⁸

In order to study further the partition of estrogens in the serum, protein-free filtrates were prepared by several methods: (1) salting out with sodium sulfate; (2) precipitation with sulfosalicylic acid; (3) ultrafiltration through celloidion membranes. The protein fraction was extracted with ether-alcohol for free estrogens. Portions of the protein-free filtrate and protein residues were hydrolyzed for conjugated estrogens and then re-extracted.

In order to determine whether splitting of the protein by other means would increase the estrogen yield, two specimens were subjected to tryptic digestion as follows: one part of serum was mixed with one part of 10 per cent trypsin in a buffer solution (pH 8.7) and incubated for 16 hours. This resulted in a digestion of approximately 70 per cent of the protein. The digested material was then repeatedly extracted with ether-alcohol and assayed for estrogen.

All specimens were assayed on adult mice of uniform size and age, seven days after castration. Four to six dosage levels were employed with each specimen and three or more animals were injected at each dosage level. The material was injected in divided doses over a three-day period. At the end of 96 hours the animals were killed, the vaginas removed and sectioned and read according to the classification of Fluhmann.⁹

Results

The estrogen content of the various sera and the extracts before and after the hydrolysis procedures are given in Table I.

TABLE I. FREE AND COMBINED ESTROGEN IN SERUM OF LATE PREGNANCY

	WHOLE SERUM FREE ESTROGEN M.U./100 C.C.	SERUM EXTRACT AFTER HYDROLYSIS AT pH 1.0 (M.U.)	RESIDUE FROM HYDROLYSIS		TOTAL ESTROGEN M.U./100 C.C.	PER CENT COM- BINED ESTROGEN
			DIRECT ASSAY (M.U.)	AFTER FURTHER HYDROLYSIS		
(1)	100	120	12	80	200	50.0
(2)	80	80	6	60	140	23.4
(3)	100	135	10	60	195	48.6
(4)	100	100	5	66	166	39.8
(5)	100	110	4	80	190	47.5
(6)	90	100	10	80	180	50.0
Hydrolysis at pH 0.5						
(7)	100	160	traces	20	180	44.4
(8)	120	200	traces	10	210	42.8
After Tryptic Digestion						
(9)	108	104			108	0
(10)	120	100			120	0

It will be observed that a small increase (up to 35 per cent) occurred in several of the sera after the initial hydrolysis at pH 1.0. However, the residue from these extracts still contained some estrogenic activity, as revealed by further hydrolysis. Moreover, small amounts could be demonstrated in water suspensions of the residue, suggesting that after initial hydrolysis a small percentage of the estrogens is ether-alcohol insoluble but water soluble. Further hydrolysis of the protein fraction resulted in considerable increase in estrogenic potency, the liberated hormone being ether-alcohol soluble. Assays of water suspensions of the residue or extracts of a third hydrolysis revealed no further increase.

The specimens which were hydrolyzed at pH 0.5 gave an increase of from 60 to 67 per cent of the free estrogenic activity after the first hydrolysis. Further extraction and hydrolysis, however, yielded only a very small increment so that the total percentage of combined estrogen was of the same magnitude as obtained with the less vigorous hydrolysis.

Digestion of the protein with trypsin failed materially to alter the estrogen content of the serum as shown in Table I.

No estrogenic activity could be demonstrated in 8 of 9 protein-free filtrates prepared by three different methods (Table II). In one instance, 20 per cent of the free estrogen content was present. Hydrolysis of this fraction failed to increase the estrogenic activity.

TABLE II. ESTROGEN IN PROTEIN-FREE FRACTION

METHOD	NUMBER OF SPECIMENS	ESTROGEN CONTENT	
		BEFORE HYDROLYSIS	AFTER HYDROLYSIS
Ultrafiltration	4	0	0
Sodium sulfate	3	0 to 20 per cent	0
Sulfosalicylic acid	2	0	0

The protein-containing residues were extracted repeatedly with ether-alcohol and yielded from 75 to 100 per cent of the free estrogenic activity. In most instances small amounts (up to 20 per cent of the free estrogenic activity) could be obtained by further extraction of the residue with water. In a number of instances, portions of this residue were subjected to further hydrolysis and yielded additional small amounts of estrogens (10 to 16 per cent of the free estrogenic activity) when extracted with ether-alcohol. Further water extraction did not increase the yield.

Discussion

Our results and those of Mühlboeck⁶ indicate that combined estrogens are present in human serum of late pregnancy. Although the proportion of combined estrogens in the serum is not nearly as great as in the urine of such patients, as much as 50 per cent of the total estrogenic content of the serum may be present in combined or conjugated form. Rather vigorous and prolonged hydrolysis, however, is required to free the combined hormone. At a pH of 1.0 it is necessary to hydrolyze and extract twice for six hours. At a pH of 0.5 a single hydrolysis for six hours frees most of the conjugated hormone. Preliminary studies in our laboratory showed that hydrolysis for less than two hours did not result in an appreciable increase of the estrogenic content. This probably explains the negative findings of Goldberger and Frank.⁸

These data indicate that the conjugated estrogens in the serum are much more resistant to hydrolysis than those in the urine, although the studies of Van Bruggen¹⁰ and of the Smiths¹¹ suggest that under certain conditions more vigorous hydrolysis procedures will markedly increase the estrogen content of the latter also.

The estrogens of pregnancy serum appear to be intimately "bound" to the protein fraction, as indicated by the fact that they do not pass through a collodion membrane, that they are precipitated with the protein fraction, that they cannot be removed completely from the latter by ether-alcohol extraction, and that vigorous and prolonged hydrolysis is necessary to liberate them completely from the latter. Tryptic digestion does not liberate the combined estrogens, suggesting that the phenomenon is not one of mere adsorption of the hormone by the protein. It is possible, however, that further digestion with other enzymes may yield different results.

Summary

1. Conjugated estrogens have been demonstrated in the serum of late pregnancy. In eight specimens examined the amount of combined hormone ranged from 23 to 50 per cent of the total estrogen content.

2. Vigorous and prolonged hydrolysis is required to free the combined hormone. For complete recovery it is necessary to hydrolyze and extract twice at pH 1.0 for 6 hours; while at pH 0.5 a single hydrolysis for 6

hours frees most of the conjugated hormone. Hydrolysis for less than 2 hours did not result in an appreciable increase in the estrogen content.

3. The free estrogen can be removed from the serum by extracting with ether-alcohol. The combined hormone can then be recovered from the residue after hydrolysis.

4. Protein-free filtrates of pregnancy serum are practically free of any estrogenic content, while almost all of the hormone can be recovered from the protein fraction.

5. The estrogens of pregnancy serum do not pass through a collodion membrane.

6. The combined estrogens of pregnancy serum are not freed by tryptic digestion.

7. The above observations indicate that the estrogens of pregnancy serum are intimately "bound" to the protein fraction.

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THE EFFECT OF MEDICAL DIATHERMY ON THE MENSTRUAL CYCLE OF THE MONKEY (*MACACUS RHEBUS*)*

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THE stimulus for the initiation of this work was the repeated clinical observation that various gynecologic procedures might be followed by successful conception and pregnancy in women who supposedly had been sterile. At various times this was observed after cervical dilatation, electrocoagulation, lipiodol patency tests¹ and medical diathermy to the pelvis. There were two women, regarded as sterile after prolonged periods of observation, who became pregnant shortly after intervals of hyperpyrexia accompanying scarlet fever. In the same category one might consider the not infrequent incidence of pregnancy in hitherto sterile women, following the coagulation or cauterization of an almost negligible cervical erosion. It was suspected that the factor common to all these procedures which affected sterility was a nonspecific physical stimulation of the pelvic organs. It, therefore, seemed worth while to study this effect under controlled conditions.

With a view to the possible ultimate application of the procedure in clinical practice, it was desirable to select a method which would do no harm if it did no good and which could be applied with the least inconvenience to the patient and the physician. Medical diathermy seemed to answer these criteria. The literature contained few references to the physiologic effects of diathermy on the generative apparatus, but those that were available were encouraging.

Thus Zocchi and Berutti² reported that short wave diathermy applied to the ovary of the rabbit resulted in an increase in the number of primordial follicles and an ovocytic stimulation in the form of Exner bodies. Lobre³ treated fifty-five women suffering from ovarian insufficiency with short wave diathermy. Of twelve women with irregular menstrual periods in the group, eight showed the establishment of a regular rhythm. In twenty-three of the women who were in various stages of the menopause, a lessening or disappearance of the circulatory and nervous disturbances was noted. One outstanding case was that of an obese, eighteen-year-old girl who had remained amenorrheic for one year despite all endocrine therapy, and who started to menstruate regularly after treatment by diathermy.

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The idea of using x-ray therapy to stimulate the ovaries was considered and discarded, even though some writers⁴ believe that it can be used with safety. In common with most clinicians, we hesitated to use this procedure because of the difficulty of drawing the line between effective stimulating dosage and destructive dosage, in any given case. We were also impressed by the report that irradiation of the germ cells in mice, not sufficient to prevent the bearing of young, could nevertheless result in abnormal and defective crania, eyes, feet, and kidneys in the progeny beyond the first generation.⁵

Material and Method

Four adult female macaque monkeys were maintained in a good state of nutrition and health in this laboratory for a period of more than a year, and were subjected to daily examination as regards the menstrual cycle and ovulation. The rectal palpation technique, as developed by Hartman,⁶ was used in conjunction with the daily vaginal smear method of Papanicolaou, as modified by Rubenstein.⁷ The two methods were found to agree in the determination of ovulation and of follicular atresia, confirming the work of Lloyd and Rubenstein.⁸

During the actual experimental period two animals were treated at a time while the other two served as controls. In this way it was hoped to avoid errors resulting from the seasonal variation in sexual function. The first two animals to be treated received diathermy for twelve days during one menstrual cycle and were observed without further treatment until all the effects of the therapy had disappeared. As it happened this required three cycles after the cycle of treatment. Thereupon the other two animals which had served as controls were treated in the identical manner to the first two, while the latter became the controls.

To avoid ambiguity it is necessary to define what is meant by medical diathermy. In this instance we mean "the use of high frequency current to produce heat in the body tissues for therapeutic purposes." As far as is known, these currents have no effects other than heat. Three varieties of medical diathermy are available, namely, the conventional long wave, the short wave by the electric field, and the short wave by electromagnetic induction. We used the conventional long wave diathermy.* It was applied by using an intravaginal electrode, and was given at thirty milliamperes for ten minutes each day, from the cessation of menstrual flow for twelve consecutive days, omitting Sundays.

Results

The results are summarized in the accompanying Table. The figures are so arranged that the corresponding data for all animals can be summated and averaged. The cycle-numbers indicate which animals were treated first and which first served as controls; they also indicate the reverse use of the animals during the second half of the experimental period. The zeros included in the columns entitled "Day of Ovulation" indicate that no ovulation occurred during those particular cycles. The figures for the totals of these same columns indicate the number of ovulations, without regard to the days upon which they occurred.

*We are indebted to Dr. Charles O. Molander, Director of the Department of Physical Therapy, Michael Reese Hospital, for advice and material assistance as regards diathermy.

TABLE I

MONKEY NO.	CONTROL				TREATED			
	CYCLE NO.	LENGTH OF CYCLE DAYS	LENGTH OF FLOW DAYS	DAY OF OVULA- TION	CYCLE NO.	LENGTH OF CYCLE DAYS	LENGTH OF FLOW DAYS	DAY OF OVULA- TION
I	5	29	5	0	①*	22	6	7
	6	29	5	0	2	20	6	8
	7	29	6	12	3	24	5	10
	8	33	4	16	4	27	6	0
II	5	27	4	12	①	21	5	7
	6	29	4	0	2	19	4	6
	7	29	5	13	3	24	5	0
	8	30	5	0	4	27	6	14
III	1	33	7	0	⑤	24	6	10
	2	30	3	15	6	20	5	7
	3	27	5	12	7	24	7	12
	4	29	5	0	8	28	5	0
IV	1	31	3	0	⑤	26	4	10
	2	30	3	0	6	20	5	8
	3	32	4	0	7	24	7	0
	4	29	3	0	8	29	3	15
Average		476	71	6		379	85	12
Total		29.75	4.44			23.69	5.31	

*O Indicates the cycle of treatment.

It will be seen that medical diathermy with an intravaginal electrode caused a definite and consistent shortening of the menstrual cycle, increase in the length of flow, and an increased number of ovulations. The average results are not due to a particularly great change in any one animal but are also true for each animal when the control and treated periods are compared. In each instance the effects of the treatment had worn off by the third cycle after the cycle of treatment. However, the general nature of the results is the same whether one, two, or three posttreatment cycles are included with the cycle of treatment, for comparison with the control periods. The consistency of the data is therefore impressive despite the small number of animals used. An incidental observation as to other results of the therapy was an engorgement of the sex skin, which acquired a much brighter color.

Summary

Four female macaque monkeys, treated with medical diathermy by the use of an intravaginal electrode, showed definite and consistent shortening of the menstrual cycles, increase in the duration of flow, and increase in the number of ovulations. In view of these results with a simple and harmless procedure, further studies on clinical patients are warranted. The possibility of stimulating the ovaries of women by such a procedure would be an important addition to our gynecological armamentarium.

We desire to acknowledge the advice and help of Dr. Samuel Soskin, Director of the Department of Metabolism and Endocrinology.

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Discussion

DR. G. W. BARTELMEZ.—In Dr. Strauss' work it is the follicular phase which appears in some instances to have been shortened, while in others it is the lutein phase. There is no indication that one phase has been more frequently shortened than the other.

A natural conclusion is that the treatment stimulated the blood flow to the ovaries as well as to other pelvic organs and this might well stir up ovarian activity. All of us who have worked with macaques know that the female generative system in this species has an inconvenient way of going into a resting state even in the midst of the breeding season. Diathermy might well start the cycles at such times.

The evidence for an increase in the number of ovulations can, however, only be regarded as suggestive. One of the animals did not ovulate in four successive cycles when untreated. It would be important to know whether this happened at the beginning, the end, or during the breeding season, as this case materially lowered the average number of ovulations in the control series.

I am unwilling to accept a diagnosis of ovulation based simply on palpation and vaginal smears. Borderline cases are common and they can be classified as ovulatory or anovulatory only by a histologic study of the ovaries. You will remember that Markee in his study of living endometrial transplants found transitions in growth rate between the two types. Hartman's work on vaginal cycles clearly showed transitions and I have many endometria which could not be classified until both ovaries had been studied.

This paper presents important findings if the conclusions can be confirmed. That would require a larger number of animals and in doubtful cases the direct inspection of the ovaries and the taking of biopsies.

DR. CARL G. HARTMAN, Urbana, Ill.—In discussing this paper Dr. Bartelmez has pointed out that the few cases presented do not, in themselves, constitute a very convincing series, especially in view of the fact that the rhesus monkey in captivity is not an altogether reliable ovulator. I agree in principle with this criticism. Nevertheless the data presented all point in the same direction and, as I wish to show in the following remarks, have the support of somewhat parallel experiments on lower mammals.

There are two aspects of the problem that readily present themselves: (1) influence of the uterus on the ovary, which involves the sequelae of hysterectomy; and (2) the effects of cervical stimulation. The former may be called humoral, the latter, neurohumoral.

Is there such a thing as "internal secretion of the uterus"? We are familiar with the influence which pregnancy exerts on the ovary, especially in its preservation of the corpus luteum for a period of time, an influence due to the placenta and not the fetus. However, we are here interested primarily in the nonpregnant, cyclically active uterine mucosa. No suspicion of remote influence has been attached to the myometrium, for the "myometrial gland" of Bouin, found in the rabbit, is not of universal occurrence.

The literature is full of references to the effects of insults to the uterus on the menstrual cycle and fertility in women, as pointed out by the essayists. Dilatation of the uterine lumen, as with a lump of paraffin, has long been known to stimulate the ovary in rat and rabbit.

But most arguments for a remote influence of the uterus on the ovary arises from hysterectomy experiments. A survey of the literature on this subject indicates that the results vary both with the species of animal used and the "species" of the experimenter. On the whole, the following remarks seem justified in summarizing this subject.

In no animal species can we depend on a serious and permanent impairment of the ovaries, unless we except the human species. That the oft-reported failing of the human ovaries as endocrine organs after hysterectomy might be explained by a peculiarly important anastomosis of uterine with ovarian arterial system in man, is not likely. In the monkey, hysterectomy has been shown not to interfere with the normal function of the ovaries (Burford and Diddle, von Wagenen and Morse). In a case of my own I removed a healthy ovary, with corpus luteum, from a monkey one year after total hysterectomy and unilateral ovariectomy. In 30 opossums, hysterectomized except for stumps of the slender cervixes, I found ovulation, corpus luteum formation and pseudopregnant swelling of the mammary glands to proceed cyclically after the operation as before. Deansley and Parks found the same for the ferret. The rat and the mouse run good cycles after hysterectomy. My former colleague, Dr. Josephine Ball, indeed, found that female rats exhibit normal heat behavior after removal of the entire genital tract above the urethral orifice.

There are, nevertheless, despite these negative findings, indications of endometrial influence on the ovaries. Sfameni reports a larger percentage of "takes" of transplanted ovaries if endometrium is transplanted at the same time. Parfenoff reduced the incidence of cystic ovaries of hysterectomized mice by means of uterine transplants. On the other hand, Leo Loeb was unable to note any effect of such transplants on the survival of the corpus luteum in the guinea pig, now to be mentioned.

Truly remarkable is the prolongation of life of corpora lutea in the guinea pig discovered by Leo Loeb; they persist for months after hysterectomy. According to Spiegel, when a guinea pig is hysterectomized prepubertally, the female matures at the normal period, ovulates once, and never again, even within a five-year period! Such corpora lutea are functional, according to Loeb, as shown by the formation of placentomata and the inhibition of ovulation.

In the rabbit, Asdell and Hammond noted a prolongation of pseudopregnancy from the normal 16 days to almost double this in the rabbit hysterectomized at the time of ovulation. It is of interest to note, further, that dilatation of the uterus in rat or rabbit, as for example, by means of a paraffin plug, definitely causes stimulation of the ovaries.

While an "endocrine" influence of the uterus may possibly be invoked to explain the results of diathermic treatment in the experiments of Strauss, Fisher and Ruben-

stein, it seems more likely that their results are due to nervous stimulation of the anterior lobe of the pituitary. The effects of such afferent nerve impulses from the vagina and the cervix to the pituitary have been clearly demonstrated at least for the rabbit and the rat.

In the rabbit ovulation is normally dependent on copulation. Ovulation will occur even though the sympathetics be removed and the animal decerebrated! On the other hand, if only the stalk of the pituitary be severed, blocking the nerve impulses from the hypothalamus, no amount of copulation will result in ovulation, but such an animal will remain in constant estrus.

The rat is well adapted for similar studies, for, as Long and Evans found twenty years ago, stimulation of the cervix with a glass rod changes the four-day cycle in a third of the cases into a long cycle of 12 to 18 days, due to the activation, via the brain and pituitary gland, of the otherwise inactive corpora lutea of the shorter cycle. If stimulated at estrus by means of a faradic current, 100 per cent of the females go into pseudopregnancy, but again only if the stalk of the pituitary remains intact. It may be added that we have brought about the identical effect by direct faradic stimulation of the pituitary, either when laid bare, or through the sella.

In these experiments we have pretty close counterparts of the cervical stimulation of the monkey cervix by diathermy. They lend plausibility to the conclusions of Strauss, Fisher and Rubenstein. They might also serve to explain the amelioration of menstrual irregularities experienced by girls after marriage. Such improvement is often a function of maturity; nevertheless, it would be interesting to find out if orgasms can be correlated to any extent with the more normal menstrual behavior.

DR. STRAUSS (closing).—I would like to answer first Dr. Bartelmez's suggestion that the variation in the number of ovulations between different animals might be a seasonal variation. In monkey No. 4 there were no ovulations and control monkey No. 3, observed in the same season of the year, had two ovulations. The second criticism was that the determination of ovulation is quite a difficult matter. The rectal palpation technique as developed by Hartman has been generally accepted by the profession as an accurate method of determining ovulation in the monkey. The vaginal smear method also is quite accepted and the two methods seemed to agree.

Both discussers thought that the animals could have derived some physical stimulation from mere handling. We did not go into detail concerning the technique, but the animals were put to sleep by means of barbiturates and then diathermy was applied after the subjects had been asleep for 15 minutes. Also, as shown in our slides, the effect of the diathermy persisted as long as three months after treatment. The control animals were stimulated in a similar manner by placing an applicator in the vagina to obtain daily vaginal smears.

VAGITUS UTERINUS

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THE patient was a woman of 35 who had previously borne two full-term babies. The first was a breech delivery and suffered an Erb's paralysis, resulting in a permanently atrophied arm. The second was delivered by high forceps and was stillborn from pressure of a forceps blade on the cord.

The patient came to the writer for the third delivery, and asked that unless the delivery could be normal it should be by cesarean section.

The external pelvic measurements were normal and the promontory of the sacrum could not be felt. Later in the second stage of labor, it was found that the pelvis was S-shaped with a high flattening.

Labor was spontaneous at term and the patient came to the hospital in very active labor. The baby was small, with head high at the pelvic brim, in occiput posterior position. Labor progressed rapidly with very strong and frequent contractions. It seemed as though delivery would be normal and quick but the head did not descend. Under complete anesthesia, the cervix was found fully dilated, with the head well engaged and still in the posterior position. This was changed easily to the anterior position. It appeared as though very slight traction from forceps might bring the head past the flattening. These were applied, but moderate tractions caused no advance.

Mindful of the promise to the patient, the forceps were removed and preparations for a cesarean section were made.

With a stethoscope on the patient's abdomen, immediately most amazing sounds were heard. Very plainly the fetus could be heard crying loudly. The sounds were high and squeaking, much like the mew of a kitten. When the crying stopped, the fetus could be heard breathing with gurgling respirations, as though choking with fluid. Both assistant and nurses listened and heard plainly the crying and breathing.

It seemed probable that the fetus would inspire too much liquor amnii, in spite of the ruptured membranes, and it was considered unwise to wait for the section. So the patient was replaced in the lithotomy position, the ether was resumed, and by internal podalic version the presentation was changed to breech. The breech extraction was performed slowly and carefully and resulted in the birth of an undamaged baby which was soon revived and crying lustily.

This delivery occurred in April, 1923. At that time a search of the literature in the New York Academy of Medicine was made for the writer by Dr. Mieczyslaw Openchowski. The data collected by him remained in possession of the writer for eighteen years. Only recently, they were checked and added to by the librarian of the N. Y. Academy of Medicine.

References were found to 131 cases of vagitus uterinus in the literature of various countries, from 1546 to 1941. One hundred and twenty-two of these were authenticated cases, all carefully verified. Nine of the very early cases were not authentic, but were merely hearsay.

In the one hundred years from 1800 to 1900, there were found in the literature 58 authentic reports of cases of vagitus uterinus, by 52 dif-

ferent authors. One reported four cases, 3 reported two each and 48 reported one each. From 1900 through 1922, there were 48 authentic cases reported by 47 authors.

Thus, at the time when the writer's case of vagitus uterinus occurred, in April, 1923, there had been 106 authentic cases reported in the literature by 99 different authors.

From the beginning of 1923 through 1940, there were found in the literature, 16 authentic cases, reported by 14 observers.

The total number of authentic cases of vagitus uterinus, therefore, in the literature from 1800 to 1941, was 122, reported by 113 authors. With the inclusion of the writer's case, not previously reported, there have been 123, reported by 114 different observers.

A few facts as gleaned from the records, may be of interest concerning these 123 babies who cried aloud before birth. Two of the babies were called abnormal, one being an anencephalic monster. Two were born after craniotomies.

The presentations among the 109 where this is mentioned were: vertex in about 69 per cent or in over two-thirds; transverse in about 15.5 per cent; breech in 11 per cent; face in about 3.5 per cent; and brow in 1 or slightly under 1 per cent.

TABLE I

TOTAL NUMBER OF AUTHENTIC CASES OF VAGITUS UTERINUS REPORTED, 123			
From 1800 to 1900— 58 by 52 authors			
From 1900 to 1923— 48 by 47 authors			
From 1923 to 1941— 17 by 15 authors			
	123	114	
Presentations of 123 Babies		Presentations of 109 Stated	
Vertex	75 or 61.0%	Vertex	75 or 68.8%
Breech	12 or 9.8%	Breech	12 or 11.0%
Transverse	17 or 13.8%	Transverse	17 or 15.6%
Face	4 or 3.2%	Face	4 or 3.7%
Brow	1 or 0.8%	Brow	1 or 0.9%
Not Stated	14 or 11.4%		109 (100.0%)
	123 (100.0%)		
Deliveries of 123 Babies		Deliveries of 108 Stated	
Forceps	50 or 40.7%	Forceps	50 or 46.3%
Versions	41 or 33.3%	Versions	41 or 38.0%
Sections	1 or 0.8%	Section	1 or 0.9%
Nonoperative*	16 or 13.0%	Nonoperative*	16 or 14.8%
Not Stated	15 or 12.2%		108 (100.0%)
	123 (100.0%)		
Fetal Mortality, 123 Babies		Mortality of 112 Stated	
Lived	91 or 74.0%	Lived	91 or 81.2%
Died	21 or 17.0%	Died	21 or 18.8%
Not Stated	11 or 9.0%		112 (100.0%)
	123 (100.0%)		
Twins	10 or 8.1%		
"Single" Babies	113 or 91.9%		
	123		
Abnormal Babies, 2			
(Anencephalic, 1)			
Craniotomies, 2			

*Mostly breech deliveries.

The deliveries of the 108 where this was stated were: by forceps in about 46 per cent; after version in 38 per cent; nonoperative (mostly breech deliveries) in about 15 per cent; and by section in 1 or slightly under 1 per cent. Thus approximately 85 per cent were born after operative deliveries.

The mortality, among the 112 where the outcome was stated, was 18.8 per cent.

Among these 123 cases of vagitus uterinus, over 8 out of 10 had operative births and the total mortality was close to 1 in every 5.

From a perusal of these cases, it is difficult to tell to what extent the crying before birth was responsible for the high mortality. The high operative incidence would seem to indicate that, whether rightly or wrongly, the attendant thought haste in delivery was necessary. However, Zitterland in 1882 cites a case of crying of the fetus 48 hours before birth, followed by a stillbirth after a normal delivery.

It is interesting to note that in the 17 more recent cases, occurring from 1923 to 1941, there were 2 fetal losses, a mortality of 11.8 per cent; and that all of the deliveries were operative, 14 by forceps, 2 after versions and 1 by section after failure of forceps.

Among the unauthenticated reports of vagitus uterinus, the earliest was by Jubus Vineelius in 1546, who mentions 2 cases.

Gerich, in a dissertation in 1719, states that there have been reported "cases of a cry or joyous exclamation heard from the abdomen of a pregnant woman." He says that Martine Weinrichius in 1551 describes a case where a child cried fourteen days before birth.

Andreas Libavius in 1596 "saw a case where the cry from the womb could be heard from quite a distance."

Others whose names are connected with vagitus uterinus are Camerarius and Nymmanus in 1628; also Semmetus who "remembers 2 cases." Sergerus in 1672 and Vaterus in 1688 both mention this phenomenon. Timaeus is quoted as regarding vagitus uterinus with pessimism but as admitting its possibility.

In Hindu medical books of Ghedda among unusual happenings, the notes may be found about Zaratusstra who is said to have been "noisy" before his birth. And according to Gerich, some fantastic stories regarding vagitus uterinus may be found in the writings of Egyptian physicians in Babylon and Assyria, in ancient Greece and Rome. It is believed that all through the Middle Ages, physicians were afraid to report such unusual cases from fear of religious persecution.

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EFFECT ON SPERMATOZOA OF TISSUE FLUIDS ENCOUNTERED IN THE FEMALE REPRODUCTIVE TRACT*

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TISSUE fluids of the female genital tract serve as the media through which the spermatozoa flagellate in their course to the ovum. Irrespective, then, of the potentialities of spermatozoa their ultimate effect may be determined largely or entirely on the compatibility with their immediate environment. These environmental fluids consist of so-called vaginal secretion, cervical secretion, uterine and Fallopian tube fluids, peritoneal fluid which undoubtedly enters the tubes, and follicular fluid surrounding the migrating ovum.

Several investigators have concerned themselves with one or more of these problems. There is general agreement among them that vaginal secretion has a deleterious effect on spermatozoa. The effect of cervical secretion has not been adequately studied, and the results previously obtained are ubiquitous.

Kugota (1929) believes uterine secretions favor locomotion of rat spermatozoa. In 1917 Dätwyler found that the life span of bull spermatozoa was reduced to one-fourth if uterine secretions were added. Ohlin (1935) was unable to determine any change with the addition of tubal extracts. Ovarian extracts, according to Dätwyler (1917) produced a slight decrease in longevity while cystic fluid increased it one-half. Löw (1902) and several subsequent workers found follicular fluid deleterious; Rendez (1929) found it beneficial in the bat and Graenzow (1932), Graper (1924), Löw (1902) attributed no effect. Hoehne and Behne (1913) believe that the peritoneal cavity and its fluid are most unfavorable to spermatozoa.

Material and Technique

Vaginal secretion was secured from the distal two-thirds of the vagina of 6 women of the gynecology department of Barnes Hospital. Four (A, C, D, E, F, Table I) had complete abdominal hysterectomies within two hours after the vaginal material was removed. None had vaginitis or leucorrhea.

The cervical secretion from these four and two other hysterectomy cases, none of which had cervicitis, was removed from the incised cervical canal and expressed from the cervical glands. Mucosal scrapings with a dull spoon were taken from the six uteri and Fallopian tubes. The

*Invaluable suggestions were made by Dr. Clarence J. Gamble of The National Committee on Maternal Health and also by Dr. T. K. Brown, St. Louis Maternity Hospital, Barnes Hospital, and Washington University Medical School.

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uteri were apparently normal except for myoma and/or prolapse. There was no salpingitis or other observed acute pathology of the tubes. These secretions, devoid of tissue, were kept at body temperature until used, i.e., 1 to 4 hours.

From several other gynecologic patients follicular fluid from unruptured nearly mature follicles, fluid expressed from the corpus luteum, and fluid aspirated from multiple ovarian cysts were collected and tested within 2 to 4 hours.

Ascitic fluid was obtained by four paracenteses of patients, two with ascites from cirrhosis of the liver and two from peritoneal metastatic carcinoma.

TABLE I. EFFECTS OF FLUIDS OF FEMALE TRACT ON SPERMATOZOA

DONORS (FEMALE)	VAGINAL SECRETION	CERVICAL SECRETION	UTERINE SECRETION	TUBE SECRETION	CONTROL
A	344	596	562	446	582
B	272	722	748	783	786
C	579	763	754	736	741
D	378	705	692	672	692
E	507	670	698	704	676
F	333	690	693	660	702
Average	402	691	697	666	696

All materials except the vaginal secretion were obtained from surgical specimens. The secretions were mixed with an equal quantity of semen and the mixture kept at body temperature. The numbers indicate the time in minutes until there was complete cessation of motion of approximately 1 million spermatozoa. The semen was secured from donors T. G. and M.; two ejaculates from each donor. Only vaginal secretion affected the longevity of human spermatozoa.

The material thus obtained was mixed with human semen, $\frac{1}{2}$ hour postejaculatory,* in 1 to 1 ratios; and these and a control of an equal fraction of the ejaculate were incubated at 37° C. At appropriate intervals fractions of each mixture as well as the control were observed microscopically for immobility of spermatozoa. When locomotion and motion had ceased in an area of the mixture approximating $\frac{1}{2}$ million spermatozoa and 1 million in the control the time was noted.†

Results

Tests on all secretions and fluids could not be made with one ejaculate. A simultaneous control test was essential, therefore, with each set of experiments. The first six series of 24 tests had an average control time of 696 minutes. Tests were made on vaginal secretion which had an average of 402 minutes or 57 per cent of the control; cervical secretion with 691 minute average; uterine fluid, 697 minutes; Fallopian tube fluid, 666 minutes. Table I details the individual tests. The second series of eight tests, which had an average control immobilization time of 675 minutes, was done on follicular fluid with an average of 800 minutes; fluid from the corpus luteum, 755 minutes; aspirated ovarian cyst fluid, 744 minutes. Table II presents the separate tests. The third series of 22 tests was designed to determine if peri-

*Approximately $\frac{1}{2}$ hour is required for the various glandular constituents of the ejaculate to become thoroughly homogeneous.

†This area with normal sperm was covered in 4 low-power diameters across a $\frac{3}{4}$ inch cover slip, two at right angles to the other two.

TABLE II. EFFECT OF OVARIAN SECRETIONS ON SPERMATOZOA

SEMEN DONORS	FOLLICULAR FLUID	CORPUS LUTEUM FLUID	CYST FLUID	CONTROL
T	793	712	750	556
G	---	760	743	694
M	807	793	740	776
Average	800	755	744	675

Semen from donors T, G, and M was mixed in 1:1 ratios with ovarian secretions and motion cessation was compared with a control. All test materials were kept at 37° C. While there is 8 to 13.5 per cent greater longevity of human spermatozoa mixed with ovarian secretions than in the control, yet that time which cannot be attributed to experimental error is apparently negligible when one considers the in vivo as compared with the experimental time of exposure to ovarian fluids.

toneal fluid at varying concentrations affected spermatozoa in any way. The results are given in Table III.

TABLE III. EFFECT OF PERITONEAL FLUID ON SPERMATOZOA

DONORS	RATIOS						CONTROL
	2:1	1:1	1:2	1:4	1:6	1:8	
I	1,206	1,010	1,185	1,180	----	1,192	1,190
J	1,025	1,030	1,042	1,032	1,024	1,030	1,033
K	1,380	1,365	----	1,330	1,360	1,330	1,350
L	1,189	1,196	1,185	1,188	1,174	1,192	1,189
Average	1,200	1,150	1,137	1,182	1,186	1,186	1,190

The initial figure in the ratio represents semen; the other, peritoneal fluid. Donors I and J had ascites from liver cirrhosis; K and L from peritoneal metastases. The semen donors were T and P. Peritoneal fluid, free from bacterial contaminants, has no effect on the longevity of the human spermatozoa.

Discussion

Significance of Results.—Probably no other uni- or multicellular organism necessarily functions in such a rapidly changing environment, as does the spermatozoon in enacting fertilization. From the male ejaculate, which is a heterogeneous composite of glandular secretions, the spermatozoa are deposited into the vaginal fornices, and rapidly migrate out of the vagina through the secretions of the cervical canal, the uterus, the Fallopian tubes, and the secretions adjacent to the ovum. The interval for this migration is approximately 69 minutes (Brown, 1943).*

Significant Effect on Spermatozoa.—Human spermatozoa are not affected deleteriously by any of the female genital tract tissue fluids except vaginal secretion. Average differences in the results lose their apparent significance when it is realized that the deviations in the individual tests are not uniform and that in general all tests, except those on vaginal secretion, closely approximate the respective control time. These variations are approximately uniformly distributed on either side of the control. Furthermore, the protracted exposures of the in vitro experiments are approximated only in the Fallopian tubes where spermatozoa may continue to live for approximately one-tenth the test time. The doubtful effects are consequently minimized.

*Any in vivo influences would have been revealed in these in vitro tests which extended over 10 times this period.

Summary

1. The human spermatozoon in traversing the female genital tract is confronted with a conduit containing several environmental tissue fluids. These fluids are consecutively vaginal *sécrétion*, cervical secretion, uterine mucosal fluid, fluid in the Fallopian tubes which include peritoneal fluid, and follicular fluid surrounding the ovum.

2. Only vaginal fluid decreases the spermicidal and aging time of the spermatozoa. The short duration of contact minimizes any effect on spermatozoa in vivo.

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INCARCERATION AND STRANGULATION OF THE CERVIX BY A RING PESSARY

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AN INTERESTING complication resulting from the use of a hard rubber ring pessary for the treatment of uterine prolapse and cystoectoele was recently seen by us. The case seems unusual enough to bear reporting.

Case Report

The patient was a 48-year-old white housewife, admitted to Kings County Hospital on June 22, 1943. Four months before, the patient had noticed "something dropping out of her," especially on walking. In the latter part of May, she sought medical advice and was fitted with a hard rubber ring pessary for support of the uterine prolapse and cystoectoele. Her complaints were relieved by the pessary, and she failed to return in two weeks for a follow-up examination.

On the evening of June 21st, the patient developed sharp, intermittent pains in the lower abdomen which steadily increased in severity. She noted slight vaginal bleeding one-half hour after onset of the pain, and concluded that this was the onset of her regular menstrual period which was expected about this time. Her previous period had begun May 28th. The lower abdominal pains eventually became so severe, however, that the patient called a local physician who referred her immediately to the hospital.

Past history revealed that the patient at 23 years of age, following delivery of her third baby, wore a pessary for three months without complication, because of a malposition of the uterus. Gravida vi, para vi. Last delivery in 1934. Menses began at 14, recurred regularly every 28 days, lasted 3 days. She usually had slight cramps during the first day of flow.

Physical examination revealed an obese, well-developed female who presented the picture of early Parkinsonism. The facies were mask-like, expressionless, and there was drooling from the mouth. Speech was slow, slurring, monotonous. A tremor of the lips was observed. Blood pressure 128/62. The general physical examination otherwise was not remarkable. Vaginal examination revealed the cervix to be presenting at the vaginal orifice. The cervix was 4 to 5 times normal size, was dark reddish-purple in color, appeared edematous and hemorrhagic, was moderately sensitive to motion. The external os could not be identified. Palpable halfway up on the portio vaginalis was a constricting hard rubber doughnut pessary, through which the cervix had herniated. The portion of the uterus proximal to the pessary was only moderately edematous.

The treatment and course were as follows: The patient was given an iced antiseptic douche for one-half hour, which caused the edema to subside moderately. The constricting pessary was then exposed by vaginal wall retractors and was split in two places, using a Liston osteotome. The patient was able to bear the necessary manipulation without an anesthetic. When the pessary had been cut in two places, the two pieces

of the pessary were easily extracted and the patient was then given a warm cleansing permanganate douche. The pessary measured $2\frac{3}{4}$ inches in diameter, with a central opening approximately $1\frac{1}{4}$ inches in diameter.

Convalescence following removal of the pessary was rapid. The patient was given a warm permanganate douche three times daily, followed by a vaginal irrigation of 3 per cent sulfanilamide solution. The swelling and gangrenous appearance of the cervix rapidly subsided. About twenty-four hours later, the cervix appeared to be only twice normal size. The external os could now be identified as a small pinhole opening. The appearance of the cervix gradually returned to normal thereafter. Only a slight superficial slough of tissue occurred, and this caused the patient no distress.

On July 1st, the cervix seemed completely healed. Pelvic examination revealed moderate relaxation of the anterior and posterior vaginal walls with large cystocele and rectocele and a first degree uterine prolapse. The external os was quite open, and the cervix was bilaterally scarred. Measurement from the posterior fornix to the pubes at this time was approximately 13 centimeters. General condition of the patient seemed satisfactory, and she was discharged to the outpatient department for further observation and treatment.

Discussion

A review of the literature revealed that the most recent case previously recorded in this country was that by Duncan¹ in 1926. He treated a 66-year-old woman who had herniated her uterus through a McIntosh stem-ring pessary while lifting a heavy weight. Following removal of the pessary, the patient made a rapid and uneventful recovery.

Vogt² likewise had observed a similar case in 1912. At that time, he was able to collect 22 cases from the German literature in which the cervix had herniated itself through the pessary lumen, but only in several of those cases did strangulation of the cervix occur.

Reins,³ Eastes,⁴ and Peters⁵ likewise have reported cases in which strangulation occurred, following herniation of the cervix through the pessary lumen.

All cases made prompt recoveries following the institution of therapy.

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55 EIGHTH AVENUE

451 CLARKSON AVENUE

THE OCCURRENCE OF ANENCEPHALIC MONSTERS IN SUCCESSIVE PREGNANCIES

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A TWENTY-EIGHT-year-old primigravida first presented herself on March 18, 1941. There was no record of monstrosities in her family. Aside from the simple diseases of childhood the patient had never been ill, never been operated on or the victim of an accident. She was married two and a half years previously and this was her first pregnancy. Her last period began on December 1st, the date of first quickening was May 5, and her expected date of confinement September 8, 1941. Her pregnancy was normal except for obvious postmaturity. On September 25 and again on October 2, medical induction of labor was attempted without result. The presentation and position were diagnosed as vertex, L.O.A., but the vertex was not easily palpable; because of this, and the evident postmaturity an x-ray plate of the abdomen was made and disclosed an anencephalic monster. Medical induction was again tried with no result. The patient was told of the abnormal condition and that she could not expect to bear a baby that would be normal and survive. She went into labor spontaneously 20 days after this, and after 14 hours of labor, the last two of which was after full dilatation, there was no further progress. She was delivered by internal podalic version and an extraction of a large stillborn anencephalic monster weighing 9 pounds and 1 ounce, 24 inches in length.

Anatomical findings at autopsy included:

1. Marked developmental skull and brain defect,
2. Bilateral pulmonary complete atelectasis,
3. Moderate post-mortem degeneration of all organs, and
4. Adrenal aplasia.

The patient on reporting for a six months' post-partum examination on May 15, 1942 was found to be about 8 to 10 weeks pregnant. Her last menstrual period was February 18, her expected date of confinement November 25, 1942. Her pregnancy proceeded in a normal manner without incident until an office visit on October 20, when this note was made, "uterus very large for an 8 months' pregnancy, fundus 41 cm. from symphysis, neither the fetal heart nor placental bruit was heard and a diagnosis of hydramnios was made." One week later on another visit, a gain in weight of $5\frac{1}{2}$ pounds was recorded and the height of the fundus was 44 cm. Because of the hydramnios and her history of previous pregnancy complicated by anencephalic monster the same complication was suspected; accordingly on November 5th, three weeks in advance of her expected date of confinement she was asked to report for an x-ray examination. It was found on her admission to the hospital that she was in labor. An x-ray examination disclosed the absence of the bones of the cranial vault and again a diagnosis was made of anencephalia. Her delivery three hours later confirmed this diagnosis. The fetus was living at birth and weighed 2 pounds, $6\frac{1}{2}$ ounces. The measured amniotic fluid was 7,800 c.c. with an estimated additional 1,500 c.c., a total of over nine liters.

Autopsy examination disclosed the following:

1. Anencephalia,

2. Pseudohemangiomatous transformation of the meninges, choroid plexus and choroid of the eye,
3. Hypoplasia of the adrenals, and
4. Prematurity.

Summary

1. The birth of anencephalic monsters occurring twice within one year to the same woman.
2. Diagnosis made in each case by roentgen ray.
3. Complication of the first pregnancy by undoubted postmaturity and a large fetus.
4. Complication of the second pregnancy by hydramnios.

26 SOUTH GOODMAN STREET

Editorial

Maternity Care for the Wives of Enlisted Men

AT A recent session of Congress a further appropriation of \$18,620,000 was provided for the medical care of the wives and children of enlisted men in the four lowest pay grades of the Armed Services. No mention is made in this supplementary measure of the standard-menacing amendment which formed the subject of an editorial in the October issue of the JOURNAL. Here again the issue of States' Rights has been abused and misused. Although the regulation of the practice of medicine is left by action of Congress in the hands of the individual States, according to our lawmakers who supported the passage of the amendment, this action fails to take into account the fact that because of the chaotic and greatly differing State laws, the responsible health officials who wish to see high standards of maternity and pediatric care maintained, will find their hands tied. For such standards, carefully developed after sincere study by the advisory consultant groups of the Federal Children's Bureau, have been set aside to permit the participation of eulists without adequate training in these fields of practice, simply because, through political pressure, State legislatures have accorded to them licensure.

A survey of the various state laws prepared and published by *Briefs*, the organ of the Maternity Center Association of New York, demonstrates the chaotic situation which now prevails.

Take the laws for example relating to chiropractic. In six States, Alabama, California, Louisiana, North Carolina, Rhode Island and Wisconsin, and in the Territory of Alaska, persons being examined for a license to practice chiropractic must be examined in obstetrics or gynecology and embryology. In five States, Illinois, Indiana, Texas, Utah, and Wyoming, obstetrics is optional with a candidate for chiropractic license. In three States, California, Nevada, and Oregon, and the Territory of Hawaii, the candidates for license to practice chiropractic must submit proof that they have had training in obstetrics. In three States, Alabama, California, and Wyoming, a license to practice chiropractic authorizes the holder to practice such methods as are taught in recognized schools. A review of the catalogues of certain chiropractic schools shows that all so far reviewed list obstetrics in the curriculum. In two States, Oklahoma and Montana, chiropractors are certified by law to execute birth certificates. Vermont authorizes the refusal of a license to practice chiropractic to a person convicted of having performed a criminal abortion. Thus, in sixteen States and two Territories, it appears from a review of State laws that chiropractors are licensed to practice obstetrics and, if the authority of the State Health Departments to set standards for what has been accepted as adequate

obstetric care cannot be invoked, these practitioners may be paid from Federal funds for the care of the wives and babies of enlisted men.

Or take the laws about naturopathy. There are eight States that have laws regulating the practices of naturopathy. California, South Carolina, Tennessee, Utah, and Washington laws specifically or by implication include the attendance of women in childbirth in the scope of naturopathic practice. Arizona, California, and Oregon require training in obstetrics and Florida requires training in midwifery as prerequisites to license. Arizona, California, and Oregon stipulate that the examination for naturopathic licenses shall include obstetrics. These cultists, with little scientific background in obstetrics, may thus be permitted to be paid from Federal funds for the care of the wives and babies of enlisted men.

The "granny" midwife, whose dangerous and superstitious ministrations have brought much unnecessary death and suffering, is licensed to practice in many States. The proponents of the amendment seem to think that there is a difference between obstetrics and midwifery but Webster's dictionary makes no distinction. It defines obstetrics as "the science of midwifery" and the usual medical definition of midwifery is "the attendance of a woman in childbirth." The twenty-one States that license midwives to practice midwifery are Alabama, California, Colorado, Connecticut, Florida, Illinois, Indiana, Louisiana, Maryland, Minnesota, Missouri, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Rhode Island, Washington, West Virginia, Wisconsin, and Wyoming, as well as the District of Columbia and Puerto Rico. Thus midwives, usually without qualifications, are licensed to care for mothers and babies and may be paid from Federal funds.

Even the State laws regarding the practice of osteopathy have loopholes, for the standards in many States have been enacted only recently. It has been stated that many osteopaths who were licensed to practice before the enactment of the present laws or who have obtained licenses by reciprocity, could not meet the educational requirements for a license now imposed by various States, if they were applying for the first time. A variety of devices have also been used to permit reregistration.

The foregoing should be sufficient evidence of the hodgepodge of medical licensure now prevailing in the United States. While it is true that examinations of candidates are stipulated in certain instances and that school attendance and training in obstetrics is a prerequisite, the question still remains, is this as a matter of fact actually provided? There are self-constituted schools of cultists, in many cases merely diploma mills or correspondence courses with no educational standards of admission, which operate entirely without the inspection and certification of our regular medical schools imposed by the American Medical Association.

The dubious education and training of the eulist groups are not based on the sound scientific principles which constitute the foundations of modern medical practice. The philosophy of practice of the leading groups depended upon the frequently unsound application of manipulative procedures for the cure of all ailments. What most of the others depended on, it is difficult to state. And now, by Congressional edict, all of the carefully developed achievements of modern obstetrics and pediatrics are to be swept aside and governmental support given to eulist procedures, unproved, untried, and essentially a source of danger to those unfortunate enough to be subjected to their ministrations. The Government insists upon the highest standards in the selection of its war material and in the training of those designated to employ it—why not apply the same principles in the care of the wives and babies of the men who are fighting to maintain a free way of life?

Department of Statistics

CONTROLLABLE FACTORS IN PUERPERAL MORTALITY IN THE BOROUGH OF BROOKLYN, CITY OF NEW YORK, WITH AN ANALYSIS OF PUERPERAL DEATHS OF 1942*

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SINCE 1936 my attention has been focused upon the trend of puerperal mortality in Brooklyn. Gratifying reductions have been made, but the problem is still challenging. The puerperal mortality rate today is not as low as in 1941, but it is still lower than the rate for the entire City of New York. Since gains will be lost unless general and personal interest is maintained, analysis of the record of each year is essential. In 1942, 130 women died of causes associated with pregnancy and childbirth; 16 of these cases were assigned to nonpuerperal causes by the Bureau of Records, Department of Health, City of New York.

Cardiac Disease

Only cardiac disease deserves special mention in this nonpuerperal group. There were 6 cases assigned to heart disease as the primary cause of death, but in 10 other cases cardiac disease was tabulated as a secondary cause. There are many important lessons to be learned from comparison of the certificates of death with the case reports in our possession. Since contributory causes like chronic myocarditis, myocardial failure associated with intestinal obstruction six weeks post partum, and cardiac failure or circulatory collapse in the course of death from eclampsia do not deserve classification as heart disease, they should not have been mentioned in the certificates of death. In other cases, deaths actually due to cardiac disease were assigned to puerperal causes that were not valid. Two examples will illustrate:

Case 1.—A primipara with rheumatic heart disease was admitted to the hospital early in the ninth month of pregnancy. Two hours later she was delivered by forceps under ether anesthesia, and died of heart failure shortly afterward. Death, really due to heart disease, was assigned to other and unspecified conditions of childbirth.

Case 2.—A primipara with rheumatic heart disease died of cardiac failure in the sixth month of pregnancy after dental surgery. Death was assigned to toxemia, though this diagnosis could not be substantiated by the case report.

We cannot change the rules for selection of the principal cause of death, but we can make sure that certificates of death are carefully written. In too many hospitals this is left to those who are completely unaware of their importance. Perhaps study of deaths in the primary cardiac group is even more important. For example:

Case 1.—A multipara with cardiac failure in the fifth month of pregnancy was sent home from the hospital in an ambulance after compensation had been restored. She was readmitted at term, delivered spontaneously and died five days later in cardiac failure.

Case 2.—A primipara who had repeatedly refused to enter the hos-

*Read at a meeting of the Brooklyn Gynecological Society, May 7, 1943.

pital, as advised by her physician, was admitted near term in cardiac failure, and died undelivered a few hours later.

We have agreed that adequate care of pregnancy complicated by rheumatic heart disease involves more than prenatal observation at frequent intervals. Prompt institution of bed rest with the first symptoms of any decrease of cardiac reserve is essential, and rest must be continuous for the duration of pregnancy, if decompensation should occur at any time in the pregnant state. Absolute bed rest is assured only in the hospital.

Puerperal Deaths

Of the total number of 130 maternal deaths occurring in Brooklyn, 114 were assigned to puerperal causes. The number of live births was 52,914 and the puerperal mortality rate is 21.5 per 10,000 live births. This rate, however, is not a true measure of the risk of pregnancy in Brooklyn, for deaths from abortion are included, while pregnancies terminating in abortion are omitted. In New York City the crude puerperal rate is based on the number of reported terminated pregnancies, 56,247, not live births; the rate so calculated is 20.3.

The corrected rate computed on the basis that each borough had the same proportion of colored pregnancies as the city as a whole, is 20.7. As heretofore, the colored population of New York City was an important statistical factor, for the puerperal death rate of colored women was more than twice that of white women, and their mortality rate from abortion eight times as high. There were twice as many deaths from abortion in Manhattan, as in Brooklyn. These rates are all provisional, but it is not expected that final data will be much different.

The confusing terminology of vital statisticians is in need of standardization. The terms used by the City of New York are very satisfactory, yet what we call the puerperal mortality rate is the maternal mortality rate of the U. S. Bureau of the Census. Yerushalmy mentions a "puerperal fatality rate" referring to the number of the deaths of women who were delivered of a live or stillbirth per 100,000 total deliveries. Likewise "pregnancy fatality rate" would refer to the ratio of abortion and ectopic deaths, and "maternal mortality rate" to the ratio of all maternal deaths to all pregnant women.

The rate for 1942 is higher than the rate for 1941, yet the trend is still downward as shown in Table I.

TABLE I. PUERPERAL DEATHS

YEAR	LIVE AND STILLBIRTHS	PUERPERAL DEATHS	PUERPERAL RATE*
1938	42,330	135	31.9
1939	42,346	110	26.6
1940	44,397	112	25.6
1941	47,820	82	17.5
1942	56,247	114	20.7

*Rates per 10,000 reported terminated pregnancies standardized for color.

The rate for 1941 was remarkably low. If this rate had prevailed in 1942, 17 women would not have lost their lives. A summary of the comparative statistics for 1941 and 1942 is presented in Table II.

Deaths in Early Pregnancy

Statistically, abortion is defined as the termination of pregnancy before the twenty-eighth week of gestation (7 lunar months) and deaths

from toxemia, trauma and hemorrhage which occur within this time period, are not assigned to these specific causes, but to abortion. Deaths due to criminal abortion, assigned to homicide before 1940, are included too. Abortion is an important factor in our mortality rate. Only 2 of the deaths were certified as criminal; 17 cases of septic abortions were said to be spontaneous though it is very likely that more accurate reporting would alter this figure. In addition, abortion appeared three times as a secondary cause in the nonpuerperal group, and in 2 of these cases, hemorrhage and shock actually caused death.

TABLE II. COMPARATIVE PUERPERAL MORTALITY

	1941	1942
Abortion	18	21
Ectopic	3	6
Hemorrhage	12	15
Toxemia	10	24
Infection	21	27
Accidents	13	14
Other	15	7

There were 6 deaths from ectopic pregnancy. There were but 3 deaths in 1941, while in 1937 there were no less than 12. Failure of diagnosis in the face of classic history and profound shock resulted in one death, and undue confidence in aqueous solutions with delay in administration of blood accounted for the death of another woman who died without operation after nine hours in the hospital.

Toxemia

The increase in the number of deaths from toxemia is striking—more than twice as many as in 1941. In addition to the cardiac death in which toxemia was reported, 2 deaths are included in which there was no toxemia at all. Errors were due to careless reporting. In one case the certificate of death read: "Uremia, bilateral polycystic kidneys; history of toxemia of pregnancy," but there had been no pregnancy for over a year. This gratuitous information was the reason why death was attributed to toxemia. In another case death was certified as due to "Post-delivery shock, stillbirth, full-term instrumental delivery, uremia." Death was probably due to rupture of the uterus. The diagnosis of uremia was based upon evidence of nitrogen retention shortly before death. There was no toxemia, yet its presence was inferred by the statistician, and death was assigned to toxemia which takes precedence over accidents of childbirth. The facts in this case are of interest. An obese, mildly diabetic patient, aged 36 years, para v, making slow progress with an unengaged vertex in R.O.P. position was subjected to three unsuccessful attempts at delivery by high forceps. Version and extraction were then carried out with great difficulty, and the placenta was removed manually. The baby weighed more than 13 pounds. She died on the sixth day post partum with symptoms ascribed to secondary shock.

There were 12 cases of eclampsia, and 4 cases of preeclampsia in this group. Prenatal care was inadequate in a large number of cases. Toxemia was reported in 4 additional cases, 3 of which are of interest: A primipara with albuminuria, whose death was assigned to infection, died of rupture of the uterus following forceps delivery; a primigravida, aged 23 years, died of pulmonary embolism following intravenous ad-

ministration of glucose solution; and a multipara, who had refused hospitalization one week earlier, died undelivered, of hemorrhage and shock due to ablatio placentae.

It is clear that this large number of deaths from eclampsia should give us considerable concern. Long emphasis on prenatal care should have brought about a more general knowledge of the symptoms which precede eclampsia. Closer attention to edema, weight and eye ground findings, and appreciation of the importance of even slight elevation of diastolic or systolic pressure levels will make the diagnosis earlier. And we all agree on the essentials of treatment—elimination of salt, limitation of fluids, bed rest and, most important of all, hospitalization. Again, it should be more clearly understood that if interruption of pregnancy or operative delivery should become necessary, local anesthesia is best, no matter what the form of intervention.

Infection

Infection was responsible for 27 deaths, or one-quarter of the puerperal deaths. According to the certificates of death, 13 deaths were caused by pulmonary embolism which has been coded as infection since 1940. At least 2 cases, however, were clearly due to hemorrhage and shock. In one case forceps failed to deliver a dead fetus, and the patient was returned to bed in shock. Two days later, she was again taken to the delivery room, still in very poor condition, and died three hours after embryotomy and manual removal of the placenta. The certificate of death read, "Puerperal embolism, forceps delivery, embryotomy, shock." In the other case, profuse hemorrhage followed forceps delivery under ether anesthesia, and manual removal of the placenta. Blood pressure fell to 50/0. The vagina was packed, and the patient was given pituitrin, ergot and 1,000 c.c. of glucose solution. Death occurred shortly after delivery. Pulmonary embolism was given as the cause of death.

Hemorrhage

In 15 cases hemorrhage was assigned as the primary cause of death. There was but one case of placenta previa, which appeared as a secondary cause, however, in 2 additional cases, and 6 cases of separation of the placenta. In the total number of 130 deaths associated with pregnancy and childbirth, more than one cause of death was mentioned in 70 cases; in 36 of these the secondary cause was puerperal. Rules for selection of the primary cause of death when joint causes have been reported may result in faulty interpretation often enough to nullify conclusions of utmost importance. Hemorrhage usually suffers more than toxemia in the application of these rules, which prefer infection over any other cause. Hemorrhage was mentioned as a secondary cause in only 4 cases of puerperal death. These very important secondary causes of death do not often appear in analyses of the causes of puerperal death. Since their implications are obvious, they are tabulated (Table III).

Accidents of Childbirth

Death was associated with accidents of labor in 25 per cent of all the cases. It appeared as the primary cause in 14 cases, and as a contributory cause in 13 additional cases of puerperal death, or 42 per cent

TABLE III. SECONDARY CAUSES OF PUERPERAL DEATH

CODE NO.	CONDITION	ASSOCIATED WITH		TOTAL
		PUERPERAL CAUSE	NONPUERPERAL CAUSE	
141	Abortion	0	3*	3
143 and 146	Hemorrhage	4	0	4
144 and 148	Toxemia	4	0	4
145 and 149	Accidents	13	7	20
150	Other	0	6	6
		21	16	37

*2 with hemorrhage.

Note that infection does not appear.

of the entire 114. This heading (code No. 149) is very comprehensive, covering injury, laceration and rupture of pelvic organs or tissue after the twenty-eighth week of pregnancy. Atony, inertia, inversion and rupture of the uterus, abnormal presentation, contracted pelvis, prolonged labor, instrumental delivery, version, cesarean section and obstetric shock are included. The more specific causes, hemorrhage, toxemia, and infection, can take precedence only when they are reported. Pulmonary embolism to which sudden death is so often attributed under these tragic circumstances is tabulated as infection.

In 20 cases in which accidents of pregnancy and childbirth were regarded as secondary causes, death was assigned to infection 7, eclampsia 3, post-partum hemorrhage 3, cardiac disease 4, and other nonpuerperal causes 4.

Cesarean section was the cause of death in 5 cases though it contributed to death in 7 additional cases. In 1937 there were 34 deaths associated with cesarean section, and in 12 of these cases the operation itself was held to be the primary cause of death. And in 1939, there were 27 deaths to which this operation contributed. At that time we concluded that this was the crux of our Brooklyn problem. It is clear that we have made progress, yet in 1942 two cesarean sections were performed after the patients had had several convulsions. In another case death was due to hemorrhage, secondary operation for hysterectomy failing to save the patient's life. In still another case, sudden hemorrhage during the operation was estimated at 800 c.c. Lost blood was promptly replaced, but the patient died of peritonitis on the fifth day after operation.

Major Cause of Death

Statistically infection (27 cases) is the leading cause of puerperal death, with toxemia (24 cases) a close second. But if to the hemorrhage figures (15 cases), are added 6 cases of death from ruptured ectopic pregnancy, 2 cases of abortion with hemorrhage and shock, and 4 cases in which hemorrhage was reported on the certificate of death, but assigned to other causes, hemorrhage equals infection in importance on the face of the figures.

Death certificates in themselves contain very little information concerning the details of birth. However, when case histories, even though brief, and possibly with important details omitted, are available, the actual causes of death are more readily discovered. A more perfect picture of the problem is seen when corrections are made for 2 cases in the toxemia group, and 2 cases of sudden death in the infection group. Other deaths assigned to accidents of childbirth as the primary cause,

or to infection with accidents as a contributory cause of death might be included as well, but they are not, only because hemorrhage was not mentioned. Yet it is likely that hemorrhage played a prominent part in every one of these deaths, and hemorrhage invites infection. Revision of the statistics of puerperal deaths shows hemorrhage as the most common cause of puerperal death in Brooklyn (Table IV).

TABLE IV. MAJOR CAUSES OF PUERPERAL DEATH
(REVISION)

	OFFICIAL	REVISION STATISTICAL	REVISION COMMITTEE
Hemorrhage	15	27	30
Toxemia	24	24	22
Infection	27	27	25

Comment

The statistical problem of joint cause selection is so difficult that deductions as to the relative frequency of any cause of puerperal death may be properly questioned. The sooner multiple cause tabulations become available, the better. From the medical point of view, the principal purpose of collecting and tabulating vital statistics is to discover the actual causes of death, so that preventive programs may be planned. It may be argued that infection, toxemia and hemorrhage are of equal importance, and that preventive effort should influence all three. But this is only partly true. Our efficiency in the management of infection has increased, for the value of chemotherapy is widely appreciated. Until the cause of the toxemias of pregnancy is known, the present fairly well-accepted ideas of prevention and treatment need but application. The public will continue to need education, as will a rapidly diminishing number of physicians. In other words, the issue is primarily educational.

The prevention of mortality from hemorrhage, however, is a simpler problem. Hemorrhage may not be the most common cause of puerperal death everywhere, but it is the most important, for it should yield to preventive measures more readily than either of the other two major causes of death. Plasma is a household word, yet plasma is not immediately available in every one of our lying-in institutions. Nor is every physician fully aware of the great progress made in our knowledge of the physiology and therapy of shock. Education is necessary, but boroughwide organization of facilities for the procurement and distribution of blood and plasma is not only necessary but practical. We will not make progress otherwise, for hemorrhage is still the outstanding controllable factor in our puerperal mortality.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology and Obstetrics

This voluminous review of **Vaginal Hysterectomy** by Kennedy and Campbell is an important contribution, as it represents the heritage and continuation of the work of Joseph Price, a pioneer in gynecological operative work, who was far ahead of his time. The book is of real importance in offering an atlas of vaginal hysterectomy by two methods, the one, the rapid clamp method (Kennedy); the other, the ligature method by Campbell. The numerous illustrations are extremely clear-cut and descriptive.

Few gynecologists realize that vaginal hysterectomy of a not greatly enlarged or fixed uterus, by means of Pryor clamps, performed by opening the posterior cul-de-sac and inverting the uterus through this opening and then incising the anterior peritoneal fold upon the finger introduced through the posterior fornix, can be accomplished and completed within three to five minutes by an expert operator, and by the same route in a somewhat longer time, if ligatures are applied. I agree fully with the authors that the postoperative morbidity and reaction under these conditions is infinitesimal compared to that following abdominal hysterectomy, no matter whether this is supravaginal or complete. According to Kennedy, over ninety-five per cent of hysterectomies performed at the Price Hospital are done by the vaginal route. This includes the removal of fibroids by morcellment, corresponding to the size of a five months' gestation. The authors do not consider antecedent ventrofixation a contraindication to vaginal hysterectomy as they have never failed to cut the resulting bands from below. They recommend vaginal hysterectomy as a routine for procidentia of the uterus, an indication with which I can in no way agree as it has been my misfortune to encounter a number of inversions of the entire vagina following this procedure, it is true, never in patients who had been operated by either of the authors.

In general I disagree completely with the indications for operation described in this volume. That every "abused cervix," as they denominate the cervix showing various nonmalignant lesions, requires removal and preferably, coincident removal of the-uterus appeals to me as much as the proposition to perform bilateral mastectomy on every patient in whom a fibroma or a cyst has been discovered. To consider the swollen, traumatized and excessive mucosa of the anterior wall a "tumorous mucous membrane" is entirely erroneous as the authors can convince themselves by putting such a patient to bed for ten days preoperatively. There is no question that under what I consider valid indications, such as the presence of an early corpus carcinoma which shows some descent, vaginal hysterectomy with plastic repair can be considered, but on the whole, their attitude appears to me to be unjustifiably radical. From the technical point of view, this book is extremely valuable.

R. T. FRANK.

Vaginal Hysterectomy. By James William Kennedy, M.D., F.A.C.S., Surgeon in Chief to the Joseph Price Hospital, Philadelphia; Consulting Surgeon to the Norristown, Coatesville and Chambersburg Hospitals, etc., and Archibald Donald Campbell, M.D., C.M., F.R.C.S.(C), F.R.C.O.G., F.A.C.S., Assistant Professor of Obstetrics and Gynecology, McGill University, Montreal; Gynecologist and Obstetrician in Chief, Montreal General Hospital, etc. Fully Illustrated. 495 pages. F. A. Davis Co., Philadelphia. 1942.

This manual on the *Mechanics of Obstetrics* by Vaux and Castallo² is an outgrowth of methods of teaching students at the Jefferson Medical College, particularly in manikin work, and is primarily intended for use of students. The material is divided into a number of chapters which deal with the pelvis and fetus, and with the diagnosis of presentations and positions.

The mechanics of obstetrics are detailed in a chapter on labor, and subsequently applied to the various normal and abnormal presentations and positions. The instrumental or manual methods to complete labors where difficulties have arisen are discussed in three chapters on forceps, version and extraction. Here the student has explained for him the work which he is presumed to do in the manikin course as well as the application of such methods in actual practice. In a chapter on multiple pregnancy the authors state "that uniovular twins are usually of the same sex."

The book concludes with a chapter on home delivery discussing the duties and responsibilities of students and the procedure of their technique while on district work in the obstetrical service.

The profuseness of the illustrations and the clarity and detail of the text, particularly on the section on mechanism of labor, should make this manual of much benefit to medical students.

PHILIP F. WILLIAMS.

The continued interest in social relations makes this third edition of *Sex in Marriage* by the Groves³ a necessary book for the physician and others who are called upon to assist as marriage counsellors of family problems. This third edition reflects the advances which have been made in endocrinology and other phases of medicine relative to these problems. One may continue to recommend this book as a part of premarital education for either man or woman.

PHILIP F. WILLIAMS.

This popular perennial *Nurses Handbook of Obstetrics* by Zabriskie appears in a seventh edition under the joint authorship of Miss Zabriskie and Dr. Nicholas J. Eastman.⁴ The interpolation herein of the viewpoint of a physician has necessitated a considerable revision of the text. There is much new material on the mechanism of labor, the newer ideas on prenatal care and, again, emphasis has been laid on public health nursing.

The arrangement of the book is such that the practical aspects are handled separately from the scientific discussion of the subject. This should make for greater value of the book as a practical working manual. Of benefit to the training school teacher of obstetrics are the suggestions after each chapter presented as conference material to promote a better understanding of what has been studied. Again, the selfevaluation tests given provide an opportunity for the individual who has studied the book to determine personally her grasp of the subject matter.

The combination of nurse and doctor authorship in this edition is an ideal one, and undoubtedly will serve to make the book a popular text in training schools.

PHILIP F. WILLIAMS.

²*The Mechanics of Obstetrics.* By Norris W. Vaux, M.D., Professor of Obstetrics, Jefferson Medical College and Mario A. Castallo, A.M., M.D., F.A.C.S., Assistant Professor of Obstetrics, Jefferson Medical College. Pages 211. Illustrations 200. F. A. Davis Company, Philadelphia, 1943.

³*Sex in Marriage.* By Ernest R. Groves, Professor of Sociology, University of North Carolina and Gladys H. Groves. Pp. 216. 5 Plates. Illustrations by Robert L. Dickinson, M.D., Past President, American Gynecological Society. Emerson Books, Inc. New York, 1943.

⁴*Nurses Handbook of Obstetrics.* By Louise Zabriskie, R.N., Formerly Night Supervisor Lying-in Hospital, New York City, and Nicholson J. Eastman, M.D., Professor of Obstetrics, Johns Hopkins University. Seventh Edition. Completely Revised and Reset. 703 pages. 376 illustrations including 15 subjects in color. J. B. Lippincott Company. Philadelphia, London, and Montreal. 1943.

Miscellaneous

Vitamins and Hormones, under the editorship of Harris and Thimann,⁵ deals with advances in researches and application of these researches. It is designed as the first of a series of yearly volumes to accumulate, correlate and digest the current literature, and has been written by various investigators well known in their special fields, and is introduced by a foreword by McCollum. The content apparently is mainly designed for workers in their special fields as the majority of articles will not be understandable or of interest to the average physician.

Of the ten articles, the one on the Appraisal of Nutritional States by Jolliffe and Most, gives an excellent summary of the situation, including much of the special work performed by these authors. Minot and Strauss discuss the Physiology of Anti-Pernicious Anemia Material. The disease is a nutritional deficiency disorder conditioned by the state of the gastric secretion. Further clarification will depend on a combination of clinical and chemical studies. The authors state that the condition "is prone to develop in blue-eyed individuals of the Nordic race, whose hair has turned prematurely gray."(!) Such presentations, for example, as the Photoreceptor Function of the Carotenoids and Vitamins A, the Growth-Factors for Protozoa, and the Intermediate Metabolism of the Sex Hormones, are of interest only to investigators along these lines. The work is of importance as a modern reference handbook.

R. T. FRANK.

The tenth volume of **Biological Symposia**⁶ serves the double purpose of presenting "Frontiers in Cytochemistry" as well as serving as a memorial volume to Professor R. R. Bensley, Emeritus Professor of Anatomy at the University of Chicago. Professor Bensley, who at the age of seventy-five is still active in research, is known for his studies on secretion, having discovered the chief neck cells of the gastric mucosa, and for having determined that the islets of Langerhans are separate organs of the pancreas, the latter discovery proving of great aid in the isolation of insulin. In addition, Professor Bensley is known as a supertechnician in histology which has been so helpful to him in his study of mitochondria.

This Symposium is based on a meeting held at the University of Chicago in 1942, and contains fourteen articles on the basic constitution of the cell, written by his pupils, coworkers and friends. Taken up are the chemical structure of cytoplasm, a study of cellular respiration, ultracentrifugal studies on cytoplasmic components, histochemical and chemical analyses, methods for isolating morphological constituents, and specific biological activities of macromolecular particles, to mention some. By the ingenious technique of Altmann-Gersh (frozen dried material), Professor Bensley's aim of separating separable parts, before analysis was attained, the mitochondria of liver cells being thus concentrated. By other methods, two other main constituents, plasmosin and ellipsin, were separated. The former is the substance associated with the variable solution-gel phenomena; the latter, ellipsin, appears to form the cell membrane. Thus these studies have advanced to a point where they throw much light not only upon structure, but upon the function of the individual parts of the cell itself. The entire book makes fascinating reading and is presented in such a fashion as to be understandable to those unfamiliar with micro-cytology.

R. T. FRANK.

⁵**Vitamins and Hormones. Advances in Research and Applications.** Edited by Robert S. Harris, Associate Professor of Nutritional Biochemistry, Massachusetts Institute of Technology and Kenneth V. Thimann, Associate Professor of Plant Physiology, Harvard University. Volume I. With a foreword by E. V. McCollum, Johns Hopkins University. 452 pages. Academic Press, Inc., New York. 1943.

⁶**Biological Symposia. A Series of Volumes Devoted to Current Symposia in the Field of Biology.** Edited by Jaques Cattell, Editor of The American Naturalist and American Men of Science. Volume X. Frontiers in Cytochemistry. The Physical and Chemical Organization of the Cytoplasm. Edited by Norman L. Hoerr, Henry Wilson Payne, Professor of Anatomy, School of Medicine, Western Reserve University. 334 Pages. The Jaques Cattell Press, Lancaster, Pa. 1943.

A monograph on the Pathology, Pathogenesis, Etiology, Diagnosis, Prognosis and Treatment of Vascular Sclerosis has appeared from the pen of Eli Moschowitz,⁷ who regrets that most treatises on arteriosclerosis are written by either pathologists or clinicians, while, according to his view, a correlation of both of these disciplines is required to understand diseases. In his discussion, he emphasizes the biology of disease processes and then turns to the mechanistic genesis of arteriosclerosis, finally discussing the psychosomatic interpretation of certain forms of essential hypertension. The monograph is designed as a working guide for the practitioner. In discussing the subject, he takes up sclerosis of the capillaries, the production of experimental arteriosclerosis by means of adrenalin, ergosterol and cholesterol. Of particular interest are the remarks on the arteriosclerosis and hypertension in the pulmonary circuit. He concludes with a chapter on therapy, in which he features educational psychological factors.

R. T. FRANK.

A large anniversary volume, in honor of Professor Pedro Belou,⁸ Professor of Anatomy at the University of Buenos Aires, has been published by his friends and colleagues. Professor Belou is particularly known for his studies on the arterial system of man. His stereoscopic atlas of the anatomy of the arteries as well as a treatise on the topographical anatomy of the arterial system, are some of his better known publications. The volume is replete with personal photographs as well as illustrations of the many festivities involved in the celebration. It likewise contains a large number of letters from famous colleagues, the world over.

R. T. FRANK.

⁷Vascular Sclerosis. With Special Reference to Arteriosclerosis. Pathology, Pathogenesis, Etiology, Diagnosis, Prognosis, Treatment. By Eli Moschowitz, A.B., M.D., Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York; Physician, Mt. Sinai Hospital, New York, etc. 178 pages. Oxford University Press, New York. 1942.

⁸Homenaje Al Profesor Pedro Belou. De Sus Ex-Colaboradores Y Miembros Del Personal Docente Y Tecnico Del Instituto de Anatomia Y I.* Catedra de Anatomia Descriptiva de la Facultad de Ciencias Medicas de Buenos Aires. En El 28.º Ano De Su Ejercicio Docente en la Catedra Universitaria. 467 pages. Guillermo Kraft Ltda., Buenos Aires. 1941.

Department of Reviews and Abstracts

Selected Abstracts

Gynecological Operations

Schwarcz, Ricardo: Contribution to the Study and Treatment of Dysmenorrhea (Menge's Metrotomy), *Bol. Soc. de obst. y ginec. de Buenos Aires* 21: 309, 1942.

Ricardo Schwarcz states that Menge based his treatment of dysmenorrhea on the concept that menstrual pain is due to a disproportion between the capacity and the contents of the uterus. He had used his method since 1916, in hundreds of patients, with complete success in 80 per cent and improvement in 10 per cent.

Under general anesthesia the uterus is dilated with Hegar dilators introduced up to the fundus and left in place for one minute each. Serious resistance is felt after No. 8 to 10 are used. Eymers's scissors, which have external cutting edges and the opening of which can be regulated to correspond to the scale of the Hegar dilators, are introduced into the uterine cavity, opened and pulled out; the internal layer of the uterine wall is thus incised in 8 to 10 different places to avoid tears of the cervical canal during subsequent dilatations up to Hegar No. 16. The largest bougies are left in place for about two minutes. Then the entire uterine cavity is tamponed with iodoform gauze soaked in sterilized oil; the tampon is removed after eight days. Roentgen examination with opaque substance before and after the operation shows the remarkable difference in the capacity of the uterine cavity.

J. P. GREENHILL

Althabe, Alberto, and Di Paola, Guillermo: Surgical Treatment of Some Forms of Ovarian Dysfunction, *Bol. Soc. de obst. y ginec. de Buenos Aires* 21: 127, 1942.

Alberto Althabe and Guillermo Di Paola describe six cases, five of which were submitted to bilateral partial resection of the ovaries and one to resection of an ovary and a half; all showed persistently favorable results. Four were sterile; all had menstrual disturbances starting with amenorrhea of varying duration, which later was complicated by irregular hemorrhages in five. The time elapsed since the beginning of the disorder varied from two to eight years during which intense hormonal treatments or curettages had been used. All patients had more or less hypertrichosis of the face, abdomen, breasts, and lower extremities; three had colostrum in the breasts and one hypertrophy of the clitoris. The basal metabolism was normal, the ovaries were enlarged, and the endometrium showed glandular hyperplasia of the adenomatous type in five and proliferation in one. The enlarged ovaries had a smooth, grayish surface through which could be seen small bluish follicles in some cases; their consistency was increased, and sagittal section revealed a thick albuginea and under it one row of follicles like a crown surrounding the considerably enlarged, hard, yellowish-gray medullary tissue.

Study of the present cases and of those reported in the literature as having responded to bilateral partial resection of the ovaries reveals that there is a typical clinical picture which seems to constitute the exact indication for this surgical intervention. In ovarian dysfunction, there are two types of patients, although both have the same principal symptoms of amenorrhea and/or metrorrhagia: in the first,

the menstrual disturbance is the only external sign of the disease; in the second, there are also other symptoms localized or not in the genital apparatus, but this type contains two subgroups. In the first, the menstrual disturbance is associated with discrete adiposity of the hips and thighs, soft skin, normal distribution of hair or hypotrichosis, normal or hypoplastic breasts, small ovaries, hypoplastic uterus and atrophic or hardly proliferating endometrium. The second is characterized by hypertrichosis, rough skin, large breasts, colostrum, normal or enlarged uterus, enlarged ovaries, glandular hyperplasia of the endometrium and more or less marked but not always constant, proximal obesity. It is this second subgroup which constitutes the indication for bilateral partial resection of the ovaries.

J. P. GREENHILL

Peterson, E.: Creation of an Artificial Vagina With the Aid of the Amniotic Membranes, *Acta obst. et gynec. Scandinav.* 21: 351, 1942.

The author reports a case of absence of the vagina in which he produced a vagina by transplanting fetal membranes. There are four similar cases reported in the literature. The result in all five cases was good. The author believes that fetal membranes are better than skin for the purpose of creating an artificial vagina.

J. P. GREENHILL

Kahanpaa, V.: High Peritonization in Gynecologic Operations, *Acta obst. et gynec. Scandinav.* 21: 357, 1942.

The author uses the term high peritonization for the procedure whereby the pelvic structures are completely isolated from the abdominal cavity by means of the sigmoid. From 1929 to 1939, 907 such procedures were performed at the Woman's Hospital in Helsinki. This method was used in every fourth gynecologic laparotomy. It was also used when raw surfaces could not be properly covered. The mortality rate in this group of cases was 0.9 per cent.

High peritonization was also used in all the infected cases, the object being to prevent the spread of infection to the general peritoneal cavity. The death rate in this group was 3.7 per cent.

By means of a follow-up letter, 84 per cent of the patients were checked. Only two of the women subsequently had to be operated on for late ileus. In women who had to be reoperated upon, there were no undue adhesions. Not infrequently the sigmoid separated from the pelvic organs to which it was attached.

In the group of women who could conceive after the operation, 45.7 per cent became pregnant. In most cases the pregnancy continued without harm.

J. P. GREENHILL

Labor

Beacham, Woodard Davis, B.A., B.S., M.D., and Varino, George Andrew, B.S., M.D.: The Management of Rupture of the Uterus Near, At, or Past Term, *Clinics* 1: 125, 1942.

Rupture of the uterus is discussed from the standpoint of incidence, mechanism of rupture, etiology, signs and symptoms of impending and actual rupture, therapy, and the treatment of shock. Four case studies are reported which present no features of particular interest except one, in which a previous low section was followed by a normal delivery and then experienced rupture of the scar during the next pregnancy. The authors have not found a similar case recorded in the literature.

HOWARD C. MOLOY

Sperl, J.: *Stenosis and Atresia of the Vagina as Obstructions to Labor*, Monatschr. f. Geburtsh. u. Gynäk. 114: 26, 1942.

In cases of vaginal stenosis and atresia associated with pregnancy, the author is opposed to prophylactic artificial abortion in the hope of preventing complications during labor. In the author's four cases the etiology was known in only one. In this case the atresia resulted from scars which followed coitus in a duplex vagina.

During pregnancy vaginal secretions and bacteria accumulate above the point of atresia and these may give rise to serious complications during labor. Therefore, the atresia should be overcome at the onset of labor. In serious cases of stricture of the vagina, rupture of the uterus may occur. Hence cesarean section should be performed. In severe cases of atresia, sterilization is advisable. In some cases stenosis may be overcome by simple incisions. Delivery can then take place through the vagina.

J. P. GREENHILL

Rouvier, M., and Gueniot, P.: *Acute Edematous Elongation of the Cervix*, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 214, 1942.

Two clinical forms have been described: (1) Unilabial polypoid edematous elongation of the cervix (Rouvier) and (2) acute total edematous elongation of the cervix (Gueniot). The partial form is characterized by a polypoid or pear-shaped tumor, its external portion the size of an orange, or larger, of violaceous color, with suffusions, and the inner part in the form of a pedicle, extending usually as far as the midportion of the anterior cervical lip. The tumor frequently appears outside the vulva, or may be palpated in the vagina. In the complete form, the elongated cervix assumes the size of a fist, shows a reddish-violaceous color and numerous submucous hemorrhages, and is slightly or not painful. The internal and external os, the much elongated cervical cavity, and the somewhat shortened fornices are preserved, the latter point aiding in differentiating the condition from a prolapse. The partial form is much more common than the complete, and both may occur during pregnancy or labor.

The same etiologic factors are probably responsible for either form; namely, contracted pelvis, multiparity, posterior cephalic presentation, prolapse, special configuration of the lower uterine segment, etc. The factors eliciting the condition include strong uterine contractions, premature descent of the presenting part, premature expulsive forces, etc., all of which may cause venous stasis. Other contributing causes, especially during pregnancy, may be systemic factors such as modification of the capillary endothelium, arterial hypertension, vasoconstriction and vasodilatation, retention of sodium chloride, inverted serum-globulin or cholesterol-fatty acid ratios, or endocrine, particularly pituitary disturbances. The symptomatology varies according to whether the patient is pregnant or in labor. During labor she is not aware of any additional pain, and the diagnosis is made incidentally. During pregnancy there may be complaints of distress in the hypogastrium and vulva, radiating to the thighs, but pain may be entirely absent. Occasionally there are discrete hemorrhages or sanguinolent discharge. The differential diagnosis includes cervical polyps, which, however, originate from the endocervix, anterior colpotelc, and hematoma or thrombus of the cervix; in the latter there is no elongation or pediculization as in Rouvier's form.

Treatment consists of reposition of the cervix maintaining it in position by dressings, and rest in bed in Trendelenburg's position. The condition tends to recur. Although there is no immediate hazard, the lesion may cause premature labor, and during delivery it may give rise to dystocia.

Gavioli presents two cases, one of each type. The cervical condition disappeared during the puerperium.

J. P. GREENHILL

Winzeler, H.: The Question of Oxytoxic Action in the Animal and Human Uteri: Basergin in the Placental Period, *Monatsschr. f. Geburtsh. u. Gynäk.* 113: 289, 1942.

The author observed that the human uterus does not react to oxytoxics in the same manner as the uterus of small animals. Hence, clinical tests in women are essential. The author maintains that basergin is the best drug for the control of post-partum hemorrhage.

J. P. GREENHILL

Westerman: Spontaneous Detachment of Cervix in Labor: *Brit. M. J.* 4: 272, 1942.

The author reports the case of a primipara with a flat type of pelvis. She was due February 10, 1942. The membranes ruptured naturally at 10:15 P.M. on February 26, and labor began. Progress was slow. She was given morphine for rest. Her pulse rate rose to 130. The blood pressure was 150/100. Head was visible at 5:30 P.M. on February 28, but receded and reappeared at 6:30 P.M. but there was no progress. She was anesthetized, and on examination, a transverse rent was found in the anterior portion of the cervix. The head was rotated and forceps delivery accomplished by delivering the stillborn fetus through the rent on February 28 after 7:30 P.M. The cord was around the neck. A ring of cervix crowning the head was delivered with it.

The author asks, "Had the nature of the condition been recognized earlier, would interference have been indicated or justifiable?"

One hesitates to comment in print on a case of this type. Fortunately the mother recovered minus the lower portion of the cervix uteri.

FRED L. ADAIR

Olivalla, José Ramirez: Retroplacental Hematoma of Pregnancy (Statistic Study, Municipal Maternity "America Arias," Havana, 1933-1941), *Rev. cubana de obst. y ginec.* 4: 186, 1942.

José Ramirez Olivalla states that this accident has occurred 62 times in 34,203 labors, or 0.18 per cent. The uncorrected maternal mortality due to the accident was 1.61 per cent. The best results were given by conservative treatment. The systematic use of abdominal surgical treatment is condemned as highly aggressive, and no case of retroplacental hematoma has been treated by the abdominal route during the last three years. Post-partum hemorrhage in retroplacental hematoma has been frequently observed; but all cases were successfully treated by the usual measures. Of the nine cases treated by abdominal surgery, four had hysterectomies. The medical treatment of the accident has avoided a considerable number of abdominal interventions which would have added an operative wound to the lesion of the uterine tissues. The author regards retroplacental hematoma as belonging to the gestoses, excluding those of mechanical origin which are exceptional.

J. P. GREENHILL

Monti, Ricardo Lopez: Pregnancy and Parturition in Myomectomized Women, *An. Inst. de Mat. y Asist. Soc.* 2: 85-104, 1940.

Ricardo Lopez Monti reports 31 cases on whom myomectomies were performed during the first months of pregnancy. He draws the following conclusions: 1. Pregnancy and parturition in women operated on for uterine fibroma progress as in nor-

mal women. 2. Prophylactic forceps at the end of the second stage, although not necessary in most cases, should be used when labor is long, when the uterine cavity was opened to remove the fibroma, or when a number of fibroids were extirpated. 3. The puerperium progressed uneventfully. 4. The operation does not interfere with fetal development. 5. Recurrence of myomas is extremely rare and does not invalidate the conservative treatment. 6. The experience of the obstetric future myomectomized women is one more argument on behalf of conservative surgery of the uterus.

J. P. GREENHILL

Bravo, Rogelio Rodriguez: Experience With Zarate's Partial Subcutaneous Symphysiotomy, *An. Inst. de Mat. y Asist. Soc.* 2: 141, 1940.

Rogelio Rodriguez Bravo reviews 63 cases observed between 1926 and 1939, and divides them into four groups: 45 operations at the Institute; four observations on patients previously symphysiotomized who had to undergo other operations for complications during subsequent labor; two observations of repeated symphysiotomy, and 12 symphysiotomized patients who later had spontaneous labors.

The author insists on careful consideration before employing symphysiotomy in primiparas because of the frequency and seriousness of the lesions which may be caused by the operation, as shown by the study of his cases. In the fourth group, he calls attention to the value of roentgen control which permits measuring the permanent separation of the pubic ligaments. Symphysiotomy should be correctly used according to Zarate's technique when it is possible to rely on good dynamics and amplitude of the soft parts to obtain spontaneous parturition; in many cases it gives the patient a dilatation that permanently solves osseous dystocia.

J. P. GREENHILL

Beruti, Josue A.: Chloral Hydrate in Labor, *Arch. Clin. obst. y ginec. Eliseo Cantón* 1: 58, 1942.

Josue A. Beruti states that his experience of 10 years with this drug shows that it fails in many cases; however, the failures must be largely attributed to incorrect indication and insufficient dosage. In correct dosage and provided that the enemas do not contain more than 3 Gm. of the drug and are not repeated too frequently, it has no disturbing effects on the evolution of labor, presents no risks for mother or fetus and has no unfavorable action on placental delivery or post-partum. Often the association of chloral hydrate and spasmalgin has an excellent effect on dilatation of the cervix.

J. P. GREENHILL

Sala, Silvestre Luis: Value of Rectal Examination in Obstetrics, *Arch. Clin. obst. y ginec. Eliseo Cantón* 1: 118, 1942.

From an extensive review of the literature and a statistic of 2,000 observations, Silvestre Luis Sala concludes that rectal examination during labor decreases puerperal morbidity, but gives less exact diagnostic information than vaginal examination. This is due to the frequently unavoidable difficulties peculiar to the method and depending on the height of the presentation. However, the index of inaccuracy in the diagnosis of the dilatation and the height of the presentation are not considerable, while vaginal examination made under aseptic conditions is not as dangerous as has been claimed. Therefore, the author recommends that rectal examination be used only to verify the progress of labor and that vaginal examination be made in the beginning and be resorted to in case of the slightest doubt, or if a more accurate diagnosis becomes necessary.

J. P. GREENHILL

Steele, Kyle B., M.D., F.A.C.S., and Javert, Carl T., M.D.: *The Mechanism of Labor for Transverse Position of the Vertex*, Surg., Gynec. & Obst. 75: 477, 1942.

The mechanism of labor in 1,300 cases was studied using frontal stereoscopic and lateral isometric roentgenographic techniques. On these 1,040 fetuses presented by the vertex, 763 begin at or above the pelvic brim, and 277 being in midpelvis. For the purposes of classification, an arc of 45 degrees (22.5 degrees on either side of the transverse) has been defined as transverse presentation. By thus broadening the criteria for this type of presentation, and also with the greater diagnostic accuracy of the x-ray, the evidence of transverse is found to be 63.4 per cent at the pelvic brim, and 62.8 per cent at midpelvis. A further extremely important point is also brought out in the finding of asynclitism in 93.2 per cent of the fetal heads at the pelvic brim and at midpelvis. The fact that 75.2 per cent showed posterior asynclitism prior to engagement, and 76.7 per cent was anteriorly asynclitic at midpelvis demonstrates the importance of the lever action of lateral flexion in affecting descent.

L. M. HELLMAN

Moia, B.: *Peripheral Circulatory Insufficiency. Collapse or Shock, With Special Reference to Obstetrical Shock*, Arch. de la Clinica obst. y ginec. 1: 319, 1942.

In the opinion of the author, in obstetrics, when collapse after childbirth occurs, it may be due to primary vasodilatation caused by stimulation of a nervous plexus in a badly performed Credé manipulation, rapid emptying of the uterus, and anesthesia, especially spinal. A second and more frequent cause of collapse is hemorrhage due to uterine atony, lacerations, placenta previa, uteroplacental apoplexy and uterine rupture. Usually, however, other factors are involved such as pain, exhaustion, dehydration, perineal trauma and toxemia.

The therapeutic measures recommended are drugs to overcome vasodilatation, blood transfusion or use of plasma. In addition, rest, sedatives for pain and the use of adrenal cortex preparations are recommended.

J. P. GREENHILL

Gynecology

Fernandes, C.: *Appendicitis in Gynecology*, An. bras. de ginec. 14: 22, 1942.

The author emphasizes that appendicitis may present itself in the form of dysmenorrhea, particularly just before menstruation. In a series of 162 patients admitted to the gynecologic department of the Brazil National Hospital with a diagnosis of appendicitis, the following gynecologic conditions were found: Seventy-nine had dysmenorrhea, twenty-two retroversions of the uterus, eighteen cervicitis, eleven genital hyperplasia, ten sterility, nine right adnexal inflammation, seven bilateral salpingitis, three left salpingitis, and three microcystic ovaries. Only eighteen failed to show some gynecologic disturbance. The author also states that from 70 to 80 per cent of women who are operated on for gynecologic conditions shows chronic inflammatory changes in the appendix.

J. P. GREENHILL

Fuerstner, Paul G.: *Reaction of Tubes and Ovaries to Induced Vascular Spasm*, Univ. California Publ., Pharmacol. 2: 105, 1942.

The important role of vascular spasm in causing local tissue change has been extensively studied in recent years. The substance most frequently used for pro-

ducing this spasm has been an extract of the posterior lobe of the hypophysis, "pitressin." Injected intravenously, it causes immediate contraction of the arterioles and capillaries. This constriction interferes with the oxygen supply to the tissues and a state of temporary anoxia is produced. Furthermore, in muscular tissue itself "pitressin" provokes spasm which contributes to the compression of the blood vessels. This tissue disturbance is followed by a compensatory dilatation of the small vessels which may or may not restore normal conditions.

Since it had been demonstrated that vascular and muscular spasms induced artificially by "pitressin" produce definite tissue changes in certain organs, the question arose whether the tissues of the female reproductive organs could be likewise influenced. Experiments were therefore carried out by Fuerstner to ascertain if, and to what degree, similar changes could be produced in these organs. Rabbits were used as experimental animals because of their fairly continuous state of estrus and their lack of spontaneous ovulation when carefully segregated.

It was found that single or repeated intravenous injections of "pitressin" (0.5 to 2.0 c.c.) produce congestion and hyperemia, and sometimes round-cell infiltration and other signs of inflammatory reaction, in the Fallopian tubes. The ovaries show a similar active hyperemia and sometimes a great increase in Call-Exner bodies. It is suggested that vascular instability, constitutional or otherwise, may result in similar changes in the tubes and ovaries of women.

J. P. GREENHILL

Da Costa Santos, Acacio: A Case of Lipschütz's Ulcus Vulvae Acutum, An. bras. de ginec. 13: 413, 1942.

The author reports a case of Lipschütz's ulcer vulvae acutum in an 18-year-old colored woman who complained of acute pain and burning sensations in the genitalia. The ulcer measured 18 by 15 cm., and was surrounded by a red areola. Examination of the material in the ulcer revealed Gram positive bacilli. Other conditions were ruled out. A cure resulted in fifteen days after the use of a stovaine paste.

J. P. GREENHILL

Defazio, Francisco: Endometrial Extracts: Uteroovarian Synergy, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 388, 1942.

Rabbits were divided into four groups: Groups I, III, and IV were hysterectomized, while group II was not operated upon. Subsequently groups II and III were not treated and groups I and IV received hormonal therapy. The animals of group I received injections of 0.20 Gm. of extract obtained from macerated homologous uteri twice weekly; those in group IV were treated by uterine grafts implanted into the abdominal wall and ear of the same animal. All animals were sacrificed after nine months.

Histological examination of the ovaries revealed that animals of the untreated group II, those of the injected group I, and those of the grafted group IV, developed hypertrophy, hyperplasia, and excessive lipoidization of the interstitial ovarian tissue with frank follicular proliferation. The ovaries of animals in group III (hysterectomized and untreated) disclosed suppression of interstitial cellular activity.

J. P. GREENHILL

Bazterrica, E., and Monzo, O. R.: Renal Ectopy as Source of Diagnostic Error in Gynecology, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 408, 1942.

Bazterrica and Monzo observed four cases of ectopic pelvic kidney, in two of which the preoperative diagnosis was ovarian cyst. The following diagnostic points

aid in differentiation of an ectopic pelvic kidney from an acquired nephroptosis. In renal ectopy the kidney pelvis is situated anteriorly, the blood vessels are multiple and inserted lower than normally and the ureter is short. In addition, the kidney frequently, though not invariably, tends to assume a round form with flattening of the anteroposterior diameter; the fetal lobulation often persists. The mobility of the ectopic kidney is of no diagnostic value for it may secondarily become fixed by perinephritic processes. The suprarenal glands do not accompany the kidney in its ectopy. Guizetti found ectopic kidneys associated with genital anomalies in about one-third of cases, and mentions particularly absence of vagina, vaginal hypoplasia, absence of the entire uterus or of the cervix alone, uterus bicornis and hypoplasia of the entire genital tract.

Clinically, bimanual palpation may elicit occasionally the presence of a tumor in thin persons when the ectopy is abdominal or iliac. In the case of a pelvic kidney, rectal or vaginal palpation may reveal the presence of a tumor, which may be lobulated. With relative frequency, the tumor reveals pulsations transmitted from the uteroovarian vessels or the abdominal aorta. Simple radiography is of value only when a calculus is present in the pelvis or calices of the kidney. There remains intravenous or retrograde pyelography as the only reliable means of establishing the diagnosis, as it indicates with clarity the localization in the pelvis and the pathologic ureteral course. The differential diagnosis includes tumors of the abdomen, pelvis, especially solid and cystic tumors of the ovary, tubes and uterus and inflammatory adnexal processes.

According to Girard, abdominal ectopy causes no complications during pregnancy, while the iliac localization may cause faulty presentations. In the pelvic variety the displaced organ may interfere with the growth of the pregnant uterus and obstruct the pelvic canal. The pressure on the uterus may cause unilateral enlargement and be the cause of rupture. Conversely the growing pregnant uterus may contribute to the increase of renal pain, or by compression, provoke retention with consequent hydronephrosis, even complete destruction of the renal tissue. During labor, the pelvic kidney may give rise to dystocia, crushing or incomplete rupture of the uterus. According to Girard, one-eighth of pregnant women with ectopic kidney abort.

J. P. GREENHILL.

Ahumada, J. C., and Sardi, J. L.: X-Ray Diagnosis of Dermoid Cysts of the Ovary, *Bol. Soc. de obst. y ginec. de Buenos Aires* 21: 252, 1942.

Odquist and Laurell, in 1925, pointed out that dermoid cysts of the ovary give a clearly delimited, rounded x-ray image, which is characterized by greater transparency than that of the surrounding soft tissues. This seemingly paradoxical finding they attributed to the great amount of fat contained within some dermoid cysts. The capsule is visualized as a thin halo of greater density than the tumor itself. The Oliver and Laurell sign apparently fell into oblivion, for only four reports since 1925 mention the abnormal transparency of the tumor (Aime, Heffernan, Galiffini, and Danelius).

To determine the factors which make x-ray diagnosis of dermoid cysts of the ovary possible, Ahumada and Sardi reviewed the clinical and anatomicopathologic records of forty-one cases seen at the Faculty of gynecologic clinics. Seven of these cases were studied radiographically. Teeth were found in six of the forty-one cases, or in 14.6 per cent. The corresponding percentage reported by various authors ranges from 18.7 to 49.0. The teeth are usually visualized at the level of Rokitsky's tubercle. As a rule they are permanent teeth, molars being more often present than incisors, and cuspids being an exception. The teeth may be rooted

within a portion of a maxilla or emerge simply from dense, fibrous connective tissue. The differential diagnosis may be difficult when only one small tooth is present, for it may be confused with an ureteral calculus. Ureteral catheterization will establish the diagnosis. Osseous formations within dermoid cysts are visualized either as bony shadows or as irregular calcifications. Such findings were present in five of the forty-one cases. In thirty-one cases the chief contents of the dermoid cyst were a vasetin-like substance, indicating that the Odquist-Laurell sign would have been positive in 75.6 per cent of the cases. It was positive in four of the seven cases studied radiographically. It is concluded that the presence of the Odquist-Laurell sign is characteristic for dermoid cysts of the ovary and can hardly be confused with any other x-ray image.

J. P. GREENHILL.

Arenas, Normand, Samartino, Rodolfo, Blanchard, Oscar, and Bettinoti, Alberto E.: *Thecoma of the Ovary*, Bol. Soc. de obst. y ginec. de Buenos Aires 21: 296, 1942.

The subject of thecoma of the ovary is reviewed and a case is reported by Arenas, Samartino, Blanchard and Bettinoti.

Thecoma of the ovary is rare, only fifty cases having been reported outside of Latin America. This is the sixth case to be reported in Brazil. The tumor appears most frequently after the age of 40; in 80 per cent of cases it occurred after the menopause had been established. The youngest patient recorded was 18. As a rule, the tumor is unilateral, lobulated, and contains a white or grayish capsule frequently transversed by dilated veins. Its outer aspect is that of fibroma of the ovary. The cut section is, however, characteristic, and shows whitish bands alternating with shiny yellow islands, and pseudocysts filled with liquefied contents of the tumor. Frozen section stained with sudan reveals a large amount of fat droplets within the cells and only a scarce amount of fat in the stroma. The tumor cells consist of fibroblasts and large fusiform, or polygonal cells, with a deeply stained nucleus and fat droplets in the protoplasm (xanthomatous cells), derived from the follicle-theca or corpus luteum. Of interest are the changes in the uterus associated with the presence of a theca cell tumor. These consist of considerable enlargement of the organ and a glandulo-cystic hyperplasia of the endometrium. This hormonal influence of the tumor on the uterus is similar to that of granulosa cell tumors.

The clinical syndrome of theca cell tumors resembles in general that common to all large abdominal tumors, namely, pressure pain, phenomena of torsion, etc. The most important diagnostic signs are ascites and hydrothorax (Meigs' syndrome) and above all the feminizing effect of the tumor. Ascites and hydrothorax were present in 35 to 50 per cent of cases. The phenomena of feminization are readily demonstrable in women past the menopause and consist of veritable rejuvenation, metrorrhagias, hypertrophy and turgescence of breasts, apparent lack of atrophy of the external genitalia and the aforementioned changes in the uterus. The feminizing effects of the tumor are obviously less conspicuous in women of childbearing age, and are manifested by menometrorrhagias, occasionally reaching pseudo-abortive proportions. The prognosis of theca cell tumors is good, only two cases with enormous ascites and pelvic metastases having been reported.

J. P. GREENHILL.

Beruti, J. D., and Palazzo, O. R.: *Results With Diathermy Electrocoagulation in Eighty-Eight Cases*, Arch. de la Clinica obstet. y ginec. 1: 395, 1942.

The authors used diathermy electrocoagulation in eighty-eight cases of persistent metrorrhagia and uterine fibroids. In the metrorrhagia cases there were 98 per cent cures and in the patients with myomatous uterine all were cured.

J. P. GREENHILL.

Fraenkel, L.: *New Aspects of the Anatomy, Physiology and Pathology of the Ovarian Theca*, *Medicina, México* 2: 321, 1942.

Fraenkel has found in women luteinized formations derived from the theca and surrounding the corpus luteum from which they are well differentiated by their color. These formations were not observed in animals, and the name of "paralutein gland" is proposed for them.

The author describes a tumor of thecal cells, with virilization and amenorrhea, which was cured by operation. In many cases, it is difficult or impossible to distinguish a real tumor from a thecal hyperplasia; therefore, he proposes the terms "thecomatosis" and "hyperthecosis." He demonstrated a thecal hyperplasia in the ovary of the newly born and places this phenomenon among the symptoms of the so-called hormonal crisis of the newly born.

J. P. GREENHILL

Rojas, E. S.: *Parametritis and Para-adnexitis*, *Ann. Inst. Pasteur* 15: 169, 1942.

The author states from personal experience that the number of these disorders has increased considerably, owing to the greater frequency of induced abortions. The manipulations used in the various social classes are the same, but their price differs; they consist of removal of the ovum, which is rarely practiced, or introduction of a sound. The cause of infection is exceptionally the gonococcus, usually the streptococcus.

The author does not attribute any importance to the causal agent because the disorder is due to the consequences of the infection and not to the infection itself. He notes the absence of fever and peritoneal symptoms and the presence of pain, dysuria and constipation; exploration reveals that all the pelvic organs are more or less inflamed without active participation of the peritoneum; the principal symptom to look for is swelling of the broad ligaments. Prognosis for life is good, for integrity of the organs doubtful, for normal function bad, and for conception practically hopeless. In the acute stage, treatment is that of puerperal fever; in the subacute and chronic stages, surgical treatment should be limited to opening collections of pus, and medical treatment consists of injections to increase the hyperleucocytosis and, especially, gynecologic massage to break up adhesions and mobilize the organs until cure is achieved.

J. P. GREENHILL

Savill, Agnes: *Pruritus Vulvae: Leukoplakia and Kraurosis*, *J. Obst. & Gynec., Brit. Emp.* 49: 5, 310, 1942.

The author makes an extensive review of the classical theories and opinions in leukoplakia and kraurosis vulvae. She concludes from her own observations that kraurosis is vulvitis occurring in elderly women or in younger women from whom the ovaries have been removed; in both cases pre-existing atrophy prevents the development of the hypertrophic stage with the keratinization seen with leukoplakic vulvitis. When foci of infection are suspected as an etiological factor, these should be cleaned up before any further treatment is carried out.

In the contracted stage of pruritus the author recommends pelvic diathermy. It is felt that it may stimulate ovarian function. The beneficial effect of diathermy is brought about rapidly, and is very enduring in true kraurosis. Estrin is of value because it softens the tissues and helps in combating local infection. In using diathermy the author stresses that it cannot cure any form of infection except that of the gonococcus; all other organisms have to be dealt with otherwise.

WILLIAM BERMAN

Eastlack, W. Lloyd, M.D.: *Stones in Female Urethra*, Virginia M. Monthly 69: 569, 1942.

Eastlack reports a case of urethral stone in a woman 41 years of age who was told that she had a small lump in the urethra 18 years previously. At this time the examination showed the "lump" was the size of a walnut. During the eighteen-year period, there had been occasional attacks of dysuria, tenesmus, and frequency which had never been severe enough to incapacitate the patient, and there had been eight pregnancies. It is emphasized by the author that the vague and relatively mild urinary symptoms are the rule in patients with urethral stone, symptoms rarely become acute. It is easy to attribute the symptoms to a mild cystitis; only when the stone reaches a very large size will severe symptoms appear, and these are usually secondary to obstruction.

Opinions of several authorities relative to the etiology of urethral stone are reviewed. It is the general consensus of opinion that most of the stones originate in a urethral diverticulum. Diagnosis is made by palpation and confirmed by x-ray and urethroscopy. Treatment consists in removal of the stone followed by removal or destruction of the diverticular sac. Through a urethroscope the stone may be crushed, washed out, the diverticulum cauterized. The author's choice is the vaginal approach in which the stone is removed, the sac excised, and the urethra reconstructed. This operation gave an excellent result in the case here reported.

WILLIAM BICKERS

Puerperium

Beruti, J. A.: *Diverse Aspects of Maternal and Neonatal Mortality*, Arch. Clin. obst. y ginec., "Eliseo Cantón" 1: 605, 1942.

Beruti calculates that throughout the world about 2,126,000 incipient lives are lost annually. At the Eliseo Cantón there were 61,718 births during the last 40 years. The total fetal mortality (stillbirths and neonatal deaths) was 9.4 per cent.

From 1901 to 1910 the fetal death rate was 12.8 per cent whereas, in the last decade it was only 7.3 per cent. The deaths are analyzed from many points of view including prematurity, deformities, death in utero, maternal illness, parity, etc. The author emphasizes particularly the high frequency of intracranial hemorrhages among the dead babies (34.3 per cent).

J. P. GREENHILL.

Moir, Chassar, and Scott, Russel C.: *An Investigation of the Effect of Ergot Alkaloids in Promoting Involution of the Postpartum Uterus*, J. Obst. & Gynaec. Brit. Emp. 50: 94, 1943.

These investigators took three series of patients. They gave the first group a routine course of ergotamine, the second group a routine course of ergometrine and the third group acted as controls. The height of the fundus was measured at 2-day intervals post partum. The results show that the average height of the fundus of patients receiving ergotamine or ergometrine is slightly higher than in the control series, though the rate of involution in the three groups is similar.

The effect of these alkaloids on the character and amount of lochia was also determined. It was found that the normal variation in the quantity and character of the lochia is very great. Records of lochial discharge do not give any trustworthy indication of the effect of drugs on the uterus. The authors also fail to find any justification for the routine use of ergot alkaloids to promote involution following uterine sepsis. It is felt that contraction of the uterus by ergot reduces the blood supply of that organ thereby reducing certain natural defense barriers against infection.

WILLIAM BERMAN.

McCausland, A. M.: The Influence of Hormones Upon Varicose Veins in Pregnancy, *West. J. Surg.* 51: No. 5, May, 1943.

Pregnant patients with varicose veins follow a clinical course suggestive of endocrine dysfunction. More particularly, the incidence of abortion in these patients is low, a third of them have definite endocrine stigmata and the varicose veins develop most often during the prenatal period when the hormone changes are most marked. The author reasons that since patients with varicose veins have a low incidence of spontaneous abortion, they should have a high progesterone level. Since progesterone is thought to relax smooth muscle elsewhere in the body, it is thought possible that the dilatation of the walls of the blood vessels may be the result of progesterone influence.

Twenty-five multiparas with mild varices were treated with 10,000 I.U. of estradiol benzoate every other day. Two other groups received 25,000 I.U. and 50,000 I.U. respectively. The authors report definite relief from disabling symptoms of varicose veins by the administration of estradiol benzoate. No effect on fetal or maternal physiology was noted.

WILLIAM BICKERS.

Leatham, James H., and Abarbanel, A. R.: The Problem of Antagonistic (Antigonadotropic) Substances to Equine Gonadotropin in Clinical Therapy, *West. J. Surg.* 51: No. 5, May, 1943.

In the opinion of the authors, equine gonadotropin is the most potent gonadotrope now available. One of its disadvantages is the development of an antagonistic substance which may be an antigonadotropic hormone. The purpose of this investigation was to determine if the increased purification of the extract would lower the tendency to the formation of antigonadotropins in the human. Twenty-one women with either a primary or a secondary amenorrhea were used for the study. Equine gonadotropin was given in doses up to 9,000 I.U. and then their sera were tested for antigonadotropin.

Antigonadotropic substances were found in the sera of six out of seven patients who had been treated with a commercial preparation. Increased purification of the equine gonadotropin (on the basis of nitrogen content) resulted in antigonadotropic substances in only one of the twelve other patients. It may, therefore, be concluded that the purified form of equine gonadotropin gives rise to less antigonadotropic substance.

WILLIAM BICKERS.

Loeser, Alfred A.: Effect of Emotional Shock on Hormone Release and Endometrial Development, *Lancet* 1: 518, 1943.

Four cases are reported in each of which a normally menstruating woman missed the menstrual period following a severe shock, three of which were due to bomb explosion in which no injury was sustained and the fourth due to fear of pregnancy. Examination of the endometrium revealed it to be at a stage of development characteristic of the day of the menstrual cycle at which the shock occurred. The author suggests that the shock produced arrest in development of the endometrium due to hormonal inhibition.

J. ROBERT WILLSON.

Wenner, R. v. Wattenwyl, H., and Joel, C. A.: Perlingual Use of Androgenic Hormones in Gynecology, *Schweiz. med. Wchnschr.* 73: 125, 1943.

In the opinion of the authors the perlingual application of methyl testosterone yields good results in the treatment of dysmenorrhea. Likewise, this form of

therapy has proved helpful in overcoming the disturbances of the menopause and painful breasts. Because of this, the authors urge the use of this type of medication.

J. P. GREENHILL.

Page, Ernest W., and Woods, Leonard: **Clinical Effects of Oral Anhydro-Hydroxy-Progesterone on the Motility of the Human Gravid Uterus**, *West. J. Surg.* 51: 225, 1943.

Anhydro-hydroxy-progesterone was given orally to ninety-three pregnant or puerperal women. An attempt was made to evaluate its effects upon uterine contractions in patients with threatened abortion. The incidence of abortion in this treated group was not different from that in the controlled group. Painful uterine contractions in the last half of pregnancy were substantially improved in fifty per cent of patients following its administration. No correlation between dosage and effect could be noted. The administration of large doses (50 to 100 mg.) did not delay the onset of labor or produce uterine inertia.

The authors conclude that the value of anhydro-hydroxy-progesterone for inhibiting uterine motility in human beings is most questionable.

WILLIAM BICKERS.

Abarbanel, A. R., Aranow, Harry, and Goodfriend, Milton J.: **Adjunctive Therapy With Diethylstilbestrol in Obstetrics and Gynecology**, *J. A. M. A.* 121: 1123, 1943.

The authors state at the outset of their article that they are going to present the preparation of diethylstilbestrol in its adjunctive field in various disorders where that preparation is now being used. The drug mentioned can therefore be only a part of a more complete rational therapeutic regimen. The following conditions are mentioned in which adjunctive therapy with diethylstilbestrol is of definite value: (1) severe climacteric vasomotor instability, (2) essential senile vulvovaginitis including generalized essential senile pruritus, (3) juvenile vulvovaginitis, (4) prevention or relief of puerperal painful engorgement of the breasts, and (5) amenorrhea, primary or secondary. Its use is of little or no value in the induction of early abortion, the suppression of lactation and the control of galactorrhea. It is also of very little value in the management of primary dysmenorrhea.

Detailed systematic studies in the human being have failed to reveal any true toxicity. It was noted that the higher the dose level the greater was the degree of nausea. This side reaction may depend a great deal on the patients' previous dietary behavior. The typical gall bladder patient may respond with a greater degree of nausea. The pregnant and the puerperal patient, and the toxemic patient may handle as much as 250 mg. of oral diethylstilbestrol a day without evident side effects.

WILLIAM BERMAN.

Rydberg, Erik, and Pedersen-Bjergaard, K.: **Effect of Serum Gonadotropin and Chorionic Gonadotropin on the Human Ovary**, *J. A. M. A.* 121: 1117, 1943.

The authors review some of the literature on the treatment of ovarian dysfunction with serum and chorionic gonadotropins. Their subject matter concerns chiefly underfunction of the ovary with its resulting amenorrhea. They have been able to produce menstruation in a great majority of their patients with secondary amenorrhea and in some patients with primary amenorrhea, and about one-half of the patients treated this way have continued to menstruate after the treatment. It was found most satisfactory to treat the patients first with serum gonadotropin and afterward with chorionic gonadotropin. The most satisfactory dosage for this stimulation therapy was 3,000 international units of serum gonadotropin given daily

for five consecutive days and then 1,500 international units of chorionic gonadotropin given every day for three days. The authors claim that in those cases that do react, menstruation makes its appearance about ten days after the last injection.

WILLIAM BERMAN.

Newborn

Baldi, E. M.: Spontaneous Rupture of Umbilical Cord During Normal Delivery, *An. Inst. de Mat. y Assist. Soc.* (Buenos Aires) 3: 80, 1941.

The author studied histologically an umbilical cord which had spontaneously ruptured during expulsion of the infant. The cord had been coiled about the neck. The cord presented an unusually large amount of Wharton's jelly which had apparently infiltrated the walls of the umbilical vessels. Illustrated.

ROBERT J. WEISSMAN.

Peschard, J. A.: Study of a Case of External (Extracranial) Hydrocephalus, *Gac. méd. de México* 73: 35, 1943.

The author undertook the care of a 50-day-old infant whose head began to enlarge with great rapidity following normal prenatal course and delivery. The only other abnormal physical finding was an enlarged liver. All motor functions were normal. Both parents and the infant were luetic. Antiluetic treatment, which had cured 4 of the author's previous cases, was of no avail and a diagnostic puncture was attempted. Fluid was freely obtained almost immediately (3 mm.) beneath the outer layers of the scalp. The circumference of the head which was 66 cm. at the onset of daily punctures was gradually reduced. The fluid contained many erythrocytes. Although the infant responded well to treatment for several weeks, it contracted enterocolitis and expired within 48 hours. No autopsy was permitted. Peschard speculates that the accumulation of fluid extracranially was a result of generalized pachymeningitis.

ROBERT J. WEISSMAN.

Henderson, J. L.: Sulphaguanidine in Neonatal Epidemic Gastroenteritis, *Brit. M. J.* 2: 410, 1943.

The author reports 102 cases of neonatal epidemic gastroenteritis occurring in six epidemics in 3 years. The lowest mortality rate for any year was 69 per cent of the infants affected. Following the institution of sulphaguanidine therapy the mortality rate dropped to 10 per cent among treated cases. The only infants who died weighed less than 4 pounds at birth. As additional treatment, the authors recommend the administration of large amounts of water by mouth and the elimination of food until recovery is well advanced.

EDITH L. POTTER.

Fiechter, N.: New Experiences Concerning the Effect of Vitamin K in the Newborn Infant, *Schweiz. med. Wehnschr.* 72: 1252, 1942.

Fiechter employed a new form of vitamin K which possesses great stability and therefore permits the preparation and storage of hypodermic solutions. The author used this new form in a large series of mothers and newborn babies and found that it restored to normal both physiologic and pathologic cases of hypoprothrombinemia. In order to secure normal prothrombin values in the newborn infant, the mother must receive 20 mg. of synkavit from 5 to 10 days before labor. The author believes that the favorable effect of vitamin K is due to the fact that it accelerates certain functions of the liver of the fetus or newborn infant.

J. P. GREENHILL.

Ballon, O.: The Prophylaxis of Hyperprothrombinemia in the Newborn Infant With Vitamin K, *Schweiz. med. Wchnschr.* 72: 1119, 1942.

The author observed that the lowest prothrombin values in the blood of newborn babies were found on the first day after delivery. In double ovum twins there was a difference in the prothrombin values, hence this fact may prove useful as a means of differentiating single from double ovum twins. The prophylactic administration of vitamin K to mothers before labor increases the prothrombin content of the blood in the newborn infant during the first week of life, usually for a short time. The author believes the origin of the K-avitaminosis of the newborn infant is due to the antagonistic influence of thyroxin on the fat soluble vitamins. The use of vitamin K in overcoming hypoprothrombinemia is a valuable procedure in the prophylaxis of hemorrhages of the newborn infant. Further aid may be expected from the use of vitamin P (Citron).

J. P. GREENHILL.

Complications of Pregnancy

Perez, M., Dixon, J., Aranovich, J., and Gori, R. M.: Cerebellar Tumor and Pregnancy, *An. del Inst. de Mat. y Assist. Soc. (Buenos Aires)* 3: 59, 1941.

A 21-year-old gravida 2 weeks after onset of pregnancy noted headaches and vomiting increasing in severity. Headache, localized in the frontal region with radiation to the occiput was not persistent, but vomiting was and had little relation to food intake. At three months, tinnitus and severe fainting episodes occurred. Neurological investigation revealed lowered muscular tonus, absence of patellar and Achilles reflexes on the right and diminution on the left. An episode of generalized clonic spasm followed by profuse perspiration was noted during the examination. The gait was staggering. Ophthalmoscopy revealed neuroretinitis gravidarum of one eye with vision diminished. The patient died suddenly, and a tumor 4 cm. in diameter was found involving the left cerebellar hemisphere and the posterior portion of the vermis. The possibility of brain tumor should always be considered in addition to the possibility of toxemia when one is confronted with unusual vomiting early in pregnancy.

ROBERT J. WEISSMAN.

Dexter, Lewis, Weiss, Soma, Haynes, Florence W., and Sise, Herbert S.: Hypertensive Toxemia of Pregnancy, *J. A. M. A.* 122: 145, 1943.

The authors find that 6 to 9 per cent of normal patients have either hypertension or albuminuria, or both, in the latter half of pregnancy. Patients with prepregnant hypertension of any degree of severity and due to any cause may have an uncomplicated course during pregnancy, a condition referred to as "hypertension uninfluenced by pregnancy." There is a high incidence of stillbirths and miscarriages in this group. From a clinical, pathologic, and laboratory standpoint, the vascular syndrome of hypertension, albuminuria, and fluid retention of pregnancy which is superimposed on a previous hypertension is indistinguishable from the pre-eclampsia and eclampsia occurring in a patient whose blood pressure and urine were normal before pregnancy.

Toxemia of pregnancy is described as a vascular disease entity closely resembling acute glomerulonephritis in its clinical characteristics. Etiologically and pathologically the two diseases differ. The symptoms result from a combination of fluid retention and hypertension. The first sign of improvement usually occurs 12 to 24 hours after delivery and consists of diuresis and loss of edema. The blood pressure falls slowly. Albuminuria diminishes in the course of days or weeks.

The only significant change in the blood chemistry is an elevation of blood uric acid. A diminution in plasma proteins is an inconstant finding. The urinary findings of albuminuria and microscopic hematuria are essential findings. The Addis counts reveal a slight increase in the number of erythrocytes, white cells and casts of all sorts.

The fetal mortality in pre-eclampsia without preceding hypertension has been reported between 5 per cent in the mild to 25 per cent in the severe cases, while in those with pre-existing hypertension it varied from 12 per cent in the mild to 69 per cent in the severe. The maternal mortality from pre-eclampsia is but a fraction of 1 per cent. Approximately 25 per cent of those with normal pre-pregnant blood pressure who develop toxemia during pregnancy are left with a permanent post-partum hypertension, and a similar percentage of hypertensive patients who develop toxemia during pregnancy have a higher blood pressure and more albumin in the urine after their pathologic pregnancy than before. It appears that the duration of the vascular disorder is more important than its severity. The authors advocate termination of pregnancy after 3 weeks of conservative therapy of a toxemia.

The earliest changes in toxemia occur in the kidneys rather than in the liver. Renal changes are diffuse and are primarily degenerative. It is a glomerulonephrosis. Liver lesions consist of capillary dilatation, hemorrhage, thrombosis, stasis, hydropic and fatty degeneration, necrosis of the hepatic cells, and lymphocytic infiltration usually at the periphery of the lobule. Focal lesions occur either in the midzone or central portion of the lobule. Infarcts are present in the placenta, the main lesions consisting of a premature aging process. There is a certain amount of syncytial degeneration.

The treatment of toxemia is prophylactic and therapeutic. The usual prophylaxis of prenatal care, dietary control, and measures to eliminate edema are essential. The use of mercurial diuretics is contraindicated. The treatment is for the most part conservative. The authors stress the importance of a too rapid fall of blood pressure in the control of eclampsia as a sign of impending disaster, and cases like this should be treated as cases of circulatory collapse.

WILLIAM BERMAN.

Dück, H.: Progesterone as a Hypotensive Drug in the Toxemias of Pregnancy, *An. Brasil de ginec.* 14: 359, 1942.

The author employed progesterone in eleven cases of toxemia of pregnancy to reduce the blood pressure. The desired aim was satisfactorily accomplished. The author believes the explanation for this phenomenon is as follows: The vascular system is so affected by progesterone that it becomes insensitive to the vaso-pressure action of the posterior pituitary hormone just as the uterine musculature is affected by progesterone.

J. P. GREENHILL.

Bazan, J., and Dubrovsky, R.: Treatment of Uncontrollable Vomiting of Pregnancy, *Semana méd.* 50: 221, Jan. 28, 1943.

The treatment of uncontrollable vomiting of pregnancy is discussed by the authors on the basis of an experience at the Instituto de Maternidad in 104 cases. Sixty-five patients were primiparas and 39 were multiparas. Eleven per cent of the patients had had previous pregnancies interrupted on account of excessive vomiting. This had occurred once in three cases, twice in five cases, three times in two cases, five times in one and more than five times in another. All of these patients were dismissed as cured, despite the additional psychologic hazard of these previous experiences.

The treatment employed consisted of isolation in the hospital, with no visitors allowed at first; psychotherapy; hydration; adequate mineral supply; sedation of the nervous system; and treatment of hepatic insufficiency. The authors stress particularly the importance of liver disturbances and the significance of urobilinuria. There is a direct relationship between hyperemesis gravidarum and urobilinuria. In simple vomiting there is no appreciable change, but if the vomiting persists, affecting the general state, the level of the urobilin in the urine becomes pathologic, varying between 1.5 and 5 mg. daily, and in one instance reached a height of 17.84 mg. Clinical improvement precedes lowering of the urobilin level, and frequently the highest value is obtained the day that the patient ceases to vomit. The decrease in urobilin is evident two or three days later, but is maintained for some weeks above the level considered as normal.

J. P. GREENHILL.

Society Transactions

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MAY 21, 1943

The following papers were presented:

Mesonephroma of the Ovary. R. J. Jensik, M.D., and F. H. Falls, M.D. (For original article, see page 810.)

The Development of the Periurethral Glands in the Human Female. John W. Huffman, M. D. (For original article, see page 773.)

The Effect of Medical Diathermy on the Menstrual Cycle of the Monkey. H. A. Strauss, M.D., L. Fisher, M.D., and B. B. Rubenstein, M.D. (For original article, see page 861.)

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF FEBRUARY 16, 1943

The following paper was presented:

Further Experience in the Management and Treatment of Carcinoma of the Fundus of the Uterus, With Five-Year End Results in Seventy-Five Patients. Lewis C. Scheffey, M.D., William J. Thudium, M.D., and David M. Farrell, M.D., Philadelphia, Pa. (For original article, see page 786.)

Items

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next written examination and review of case histories (Part I) for candidates will be held in various cities of the United States and Canada and by special arrangements at Army and Navy Stations on Saturday, February 12, 1944 at 2:00 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications for this year's examinations must be in the office of the Secretary by November 15, 1943.

Arrangements will be made so far as possible for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or by a Medical Officer designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates in Military Service who wish to do so may send their case records in advance of the examination date to the office of the Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may be ordered to Detached Duty for the purpose of taking these examinations whenever possible. The Office of the Surgeon General of the U. S. Navy presumably takes a similar attitude on this matter.

The place of the Board's Part II examination in May or June 1944 has not yet been decided, but it is likely to be held in that city nearest to the largest group of candidates. The exact time and place will be announced later.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, so that his plans are thus interrupted, deferment of parts of these without time penalty will be granted under a waiver of our published regulations covering civilian candidates.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

PAUL TITUS, M.D.

SECRETARY.

OCTOBER 19, 1943.

Announcement is made that the Directory of Medical Specialists is now to be published by the A. N. Marquis Company of Chicago. Previous editions have been published for the Advisory Board for Medical Specialties by the Columbia University Press of New York City.

It is planned not to issue the next edition before 1945, on account of the war, but the A. N. Marquis Company will publish a supplemental list of all those who have been certified by the American Boards since the last (1942) edition of the Directory, totaling about 3,600. This is to be distributed at cost, and monthly or bimonthly bulletins listing successful candidates for certification at examinations during the additional interim before the next edition, are to be issued as a subscribers' service.

Dr. Paul Titus (Pittsburgh) of the American Board of Obstetrics and Gynecology will continue as the Directing Editor, and Dr. J. Stewart Rodman (Philadelphia) of the American Board of Surgery continues as Associate Editor. The Editorial Board will be composed, as before, of the Secretaries of the fifteen American Boards.

Communications should be addressed to the Directing Editor, Directory of Medical Specialists, 919 No. Michigan Avenue, Chicago (11), Illinois.

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